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ISBN 0-315-55558-0

Canada

THE UNIVERSITY OF ALBERTA

STUDIES OF BASIC PROPERTIES OF SEVERAL BENZIMIDAZOLES

by

KINGSLEY K. DONKOR

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL 1989

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in partial fulfilment of the requirements for the degree of

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ABSTRACT

Nonaqueous titrations are frequently desirable or required because of the increased sensitivity, improved selectivity or greater solubility achieved with nonaqueous solvents. Benzimidazole and some substituted benzimidazoles have been determined in acetic acid medium by weight titrations, with perchloric acid as titrant. End points were determined both with visual indicators and by automatic potentiometric titrations. Results obtained by these two end point methods were compared and found to be in good agreement. The suitability of the two visual indicators, α-naphtholbenzein and crystal violet, was assessed by comparison with potentiometric end point detection by an inverse-derivative plotting method. All methods gave the same results within experimental error.

The basic strengths of five benzimidazoles were determined by measuring spectrophotometrically their ionization constants at different ionic strengths. Two extrapolation techniques for determining thermodynamic pK_a values, log K *versus* μ and log K *versus* $\mu^{1/2}$, were compared. Of the two, plots of log K *versus* μ were found to be more linear and also to give thermodynamic pK_a values which are in better agreement with literature values for previously measured benzimidazoles.

ACKNOWLEDGEMENTS

I would like to express my heartfelt thanks to Dr. Byron Kratochvil for his continuing encouragement, support and guidance in this research project, which made working under him technically exciting and a personal pleasure.

I also express my sincere gratitude to Dr. Rod Olsen of Hamline University, St. Paul, Minnesota, for his generous assistance and helpful suggestions.

My sincere thanks also to Miss Annabelle Wiseman for the diligent typing of this manuscript and to Lawrence Amankwa for his invaluable help.

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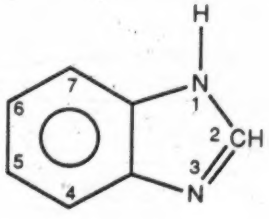
CHAPTER I
INTRODUCTION

1. NOMENCLATURE

The ring system in which a benzene ring is fused to the 4,5-positions of imidazole is designated as benzimidazole. The various positions on the benzimidazole ring are numbered in the manner indicated.

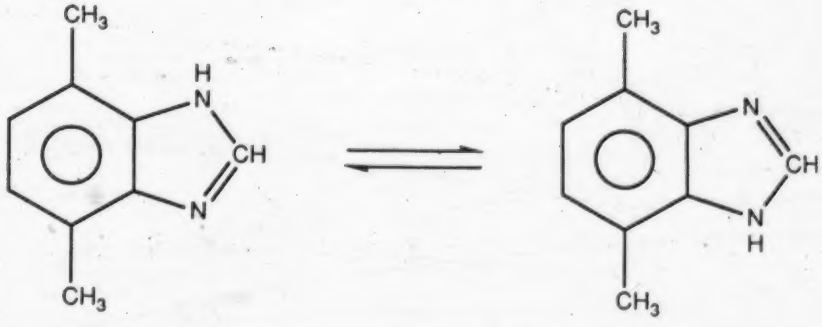


Benzimidazoles possessing a free imino hydrogen are tautomeric systems. The two possible tautomeric forms of benzimidazole (and those of its derivatives possessing a plane of symmetry) are identical, and a definite assignment of structure is possible. Examples are 2-methyl-, 5,6-dimethyl-, and 4,7-dimethylbenzimidazole [1].

2-methylbenzimidazole

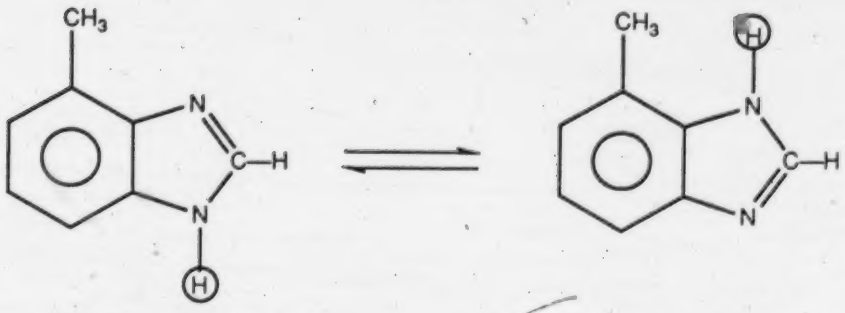
5,6-dimethylbenzimidazole

4,7-dimethylbenzimidazole



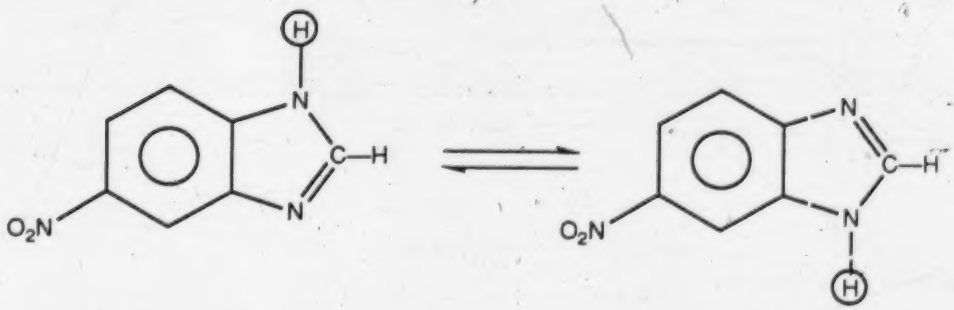
Mono- and poly-substituted benzimidazoles not possessing a plane of symmetry may behave as though they were composed of two compounds, thus rendering impossible a definite assignment of structure. 4-Methylbenzimidazole, for example, is tautomeric with 7-methylbenzimidazole and, consequently, must be designated as 4(or 7)-methylbenzimidazole. A similar situation prevails in the case of 5-nitrobenzimidazole which is tautomeric with 6-nitrobenzimidazole and, thus, is designated as 5(or 6)-nitrobenzimidazole. The same considerations apply to the more highly substituted benzimidazoles.

4(or 7)-methylbenzimidazole



4-methylbenzimidazole 7-methylbenzimidazole

5(or 6)-nitrobenzimidazole



5-nitrobenzimidazole 6-nitrobenzimidazole

Substitution of the imino hydrogen eliminates the possibility for tautomerism, and a definite assignment of structure becomes possible. The numbering starts at the substituted nitrogen [1].

2. SPECTROSCOPIC PROPERTIES

2.1 Infrared Spectra

Spectra of simple alkyl benzimidazoles in the solid phase are characterized by a series of strong, broad bands in the region of 2400 to 3200 cm^{-1}. They have no band in the region normally associated with the N—H stretching vibration. On the other hand, in solution this broad absorption is replaced by a single sharp band near 3400 cm^{-1}, which may be ascribed to the N-H stretching vibration. By examination of 1-deuterobenzimidazole in the solid phase, it has been shown that the strong bands near 2400 to 3200 cm^{-1} are best assigned to strong hydrogen bonds of the type N——H ····N.

The 1650 to 1500 cm^{-1} region is particularly characteristic for benzimidazoles. All substituted derivatives have bands in this region that vary in position and intensity with the nature and position of the substituent.

In general, groups attached to the rings of benzimidazole show their normal characteristic bands. However, some of these vibrations may be modified by the imidazole ring if a strong electronic interaction occurs. For example, in 2-acetylbenzimidazole the carbonyl absorption at 1664 cm^{-1} is typical of α,β-unsaturated ketones [2].

2.2 Ultraviolet Absorption Spectra

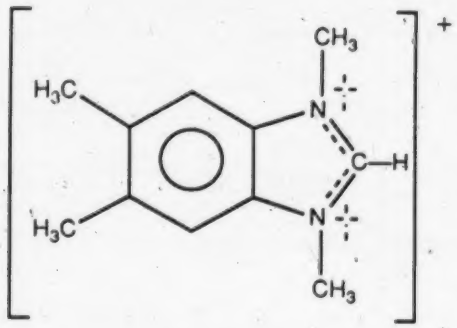
The benzimidazoles possess characteristic absorption spectra in the ultraviolet region which may be of use for their identification [1]. The absorption pattern of benzimidazole resembles that of a substituted benzene derivative; the short- and long-wavelength absorption bands at 240 and 280 nm correspond to transitions in the imidazole and aryl rings respectively [1].

The spectra of 2-alkyl derivatives are similar to benzimidazole, but substitution of alkyl groups in the aryl ring causes small bathochromic (red) shifts of all bands. An electron-withdrawing group such as acetyl in the 2-position modifies the spectrum considerably. An intense band appears at 300 nm, and the 240-nm band shows a hypsochromic (blue) shift. In the spectra of 4- and 5-nitro derivatives a new band appears near 300 nm and a regression of the shorter wavelength band occurs [3]. In contrast to the effects of other substituents (*eg.* methyl [4]), a larger bathochromic shift is noted for the 4-isomer. Such behavior is rationalized by Leandri and coworkers [5] by consideration of the compounds as a nitrobenzene system slightly modified by different substitution patterns.

In dilute hydrochloric acid solution the benzimidazole ring is protonated to form the appropriate benzimidazolium ion, and this is usually manifested by small hypsochromic shifts in spectra compared to those in ethanol; an exception to this general rule is noted for 4,7-dimethoxy derivatives [6]. Conversely, in dilute basic solution where salt formation should occur, it might be expected that bathochromic shifts would be observed. This is certainly the case for 4- and 5-nitro- and 2-acetyl benzimidazole, but in most cases only very small shifts occur, although some loss of fine structure is observed [2].

Spectra of the benzimidazoles exhibit a number of bands in acid solution which are shifted in a characteristic manner in alkaline medium. The difference in the electron distribution between the uncharged benzimidazole and the corresponding benzimidazolium ion must be responsible for the marked shifts in the absorption spectra. This explanation is supported by the observation that the ultraviolet absorption spectrum of quaternary

benzimidazolium ions such as 1,3,5,6-tetramethylbenzimidazolium ion is not dependent on pH. The possibility of proton additions is non-existent in this type of compound [1].



1,3,5,6-tetramethylbenzimidazolium ion

2.3 Fluorescence Spectra

Fluorescence spectra of benzimidazole and some of its derivatives have been recorded in neutral and acidic solution [7-11]. Neutral molecules of benzimidazole show an emission band near 290 nm, whereas the cation gives rise to a broad structureless band with a maximum near 360 nm [9]. Derivatives of benzimidazole such as 2-alkyl compounds also show an emission maximum near 300 nm, but more complex behavior is evident in acid solution where benzimidazolium ion formation occurs; for these cases emission bands near 290 and 360 nm may or may not occur depending on the type and position of the substituent [10].

2.4 Nuclear Magnetic Resonance Spectra

Because of the tautomeric equilibrium in the heterocyclic ring of benzimidazole, the aromatic ring proton resonances appear as AA'BB' multiplets in nuclear magnetic resonance [NMR] spectra [12]. Only small differences in chemical shift values are observed when the 1- and 2-positions of benzimidazole are substituted by methyl [13] and alkylsulfonyl [14] substituents.

In dilute sulfuric acid, benzimidazole is protonated to form the benzimidazolium ion, but a rapid proton exchange with solvent occurs [15]; in concentrated sulfuric acid this process is considerably decelerated, and in this medium H-2 appears as a triplet with $J_{12}=J_{23}$ = 2.5-2.6 Hz [15,16].

NMR data for benzimidazole in acidic solutions, together with comparative data for the free base are as follows: benzimidazole in CD_3OD has δ values, 7.61 (4H, 7H); 7.24 (5H, 6H); 8.14 (2H); benzimidazole (HCl) in CD_3OD δ values are 7.88 (4H, 7H), 7.66 (5H, 6H), 9.50 (2H) and benzimidazole in H_2SO_4 has values 9.01 (2H), 11.84 (1H,3H), with coupling constants $J_{12}=J_{23}$ = 2.6. The low-field shift observed on passing from the free base to the benzimidazolium ion [17] is characteristic for other heterocyclic compounds; conversely, small high field shifts are noted in the NMR spectra of solutions of the sodium salts of benzimidazole and its methyl derivatives [18].

3. GENERAL PROPERTIES

3.1 Boiling Points, Melting Points and Degree of Association

The fundamental properties of the benzimidazoles, such as melting and boiling point characteristics, the degree of association, the amphoteric nature and tautomeric behavior parallel closely those of simple imidazoles. The

benzimidazoles are high melting and high boiling solids. The parent compound melts at 170°C. They are sparingly soluble in nonpolar solvents and quite insoluble in polar solvents like water.

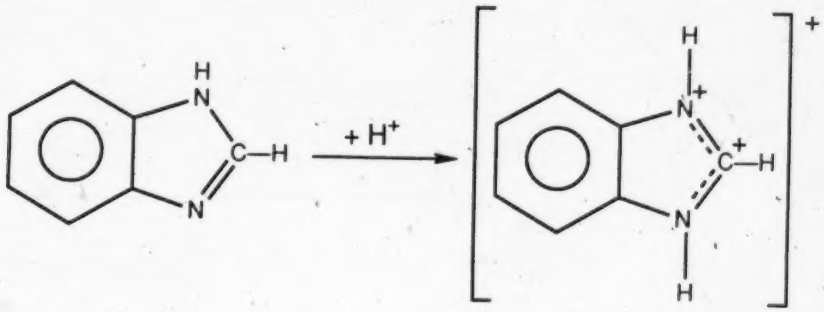
Benzimidazoles possessing a free imino hydrogen have markedly lower boiling and melting points, and the N-substituted benzimidazoles are not significantly associated. Benzimidazoles embodying the necessary structural prerequisites for intramolecular hydrogen bonding are likewise not markedly associated [1].

3.2 Pseudoacidic Character

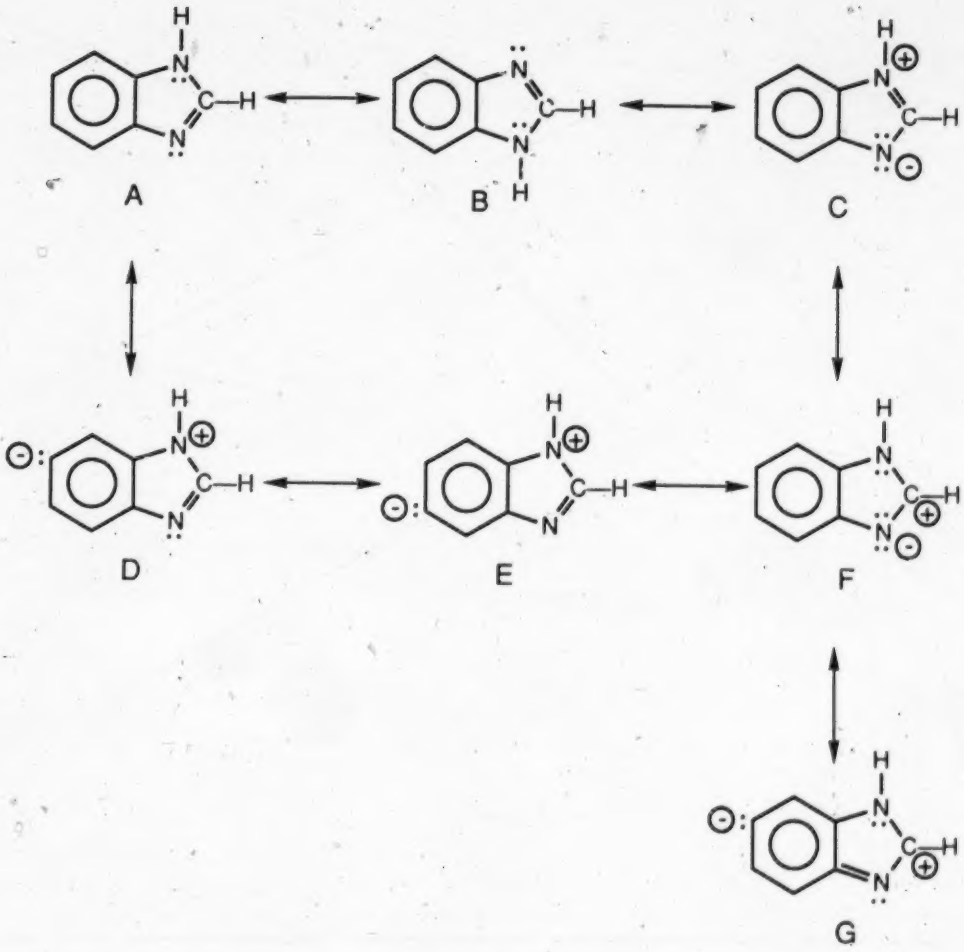
The pseudoacidic character of benzimidazole and many of its derivatives is reflected in the ability to form salts with metals. Most important among these is the sparingly soluble silver salt which forms when a solution of silver nitrate is added to a solution of benzimidazole in boiling water [19-21]. It is a crystalline solid which dissolves readily in dilute mineral acids or acetic acid. Sparingly soluble precipitates are also obtained with ammoniacal solutions of copper, cobalt, cadmium, and zinc ions. 2-Methyl-, 2-phenyl-, 2-methoxymethyl-, 2-ethoxymethyl-, 2-phenoxymethyl-, 2,5(or 2,6)-dimethyl-, 5(or 6)-bromo-2-methyl and 5(or 6)-nitro-2-methylbenzimidazole are capable of forming silver salts but fail to give precipitates with the other metal ions mentioned [21]. The ability to react with Grignard reagents to give N-magnesium halides also reflects the acidic nature of the benzimidazoles [22]. Substitution of the imino hydrogen eliminates the pseudoacidic properties.

4. BASIC STRENGTH AND ELECTRONIC STRUCTURE

The benzimidazoles are predominantly basic compounds having the ability to form salts with acids. The basic properties result from the ability of the imidazole nitrogen to accept a proton.



Benzimidazole (pK_a = 5.5) is a base considerably weaker than imidazole (pK_a = 7.0). This difference in basic strength is a reflection of the conjugation between the imidazole and benzene rings. Conjugation increases the number of contributing states in the chemical stability of the molecule. Concurrently, it tends to remove electrons from the pyridine nitrogen, thus decreasing its proton affinity. Structures A to G may represent the major contributions to the state of the benzimidazole system [1].



Structures D, E and G picture the conjugation between the imidazole and benzene portions which may be responsible for the difference in basic strength between imidazole and benzimidazole.

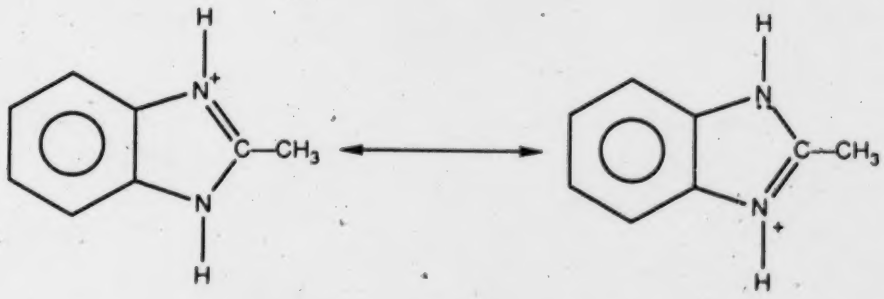
Table 1 summarizes the basic strength (in pK_a units) of a variety of substituted benzimidazoles, both in water and in 50 percent aqueous ethanol [23].

Table 1. pK_a Values of Benzimidazole and Some Substituted Benzimidazoles at 25°C in Water and 50% Ethanol (from Ref. 1) and at 30°C in 5% Ethanol (from Ref. 24).

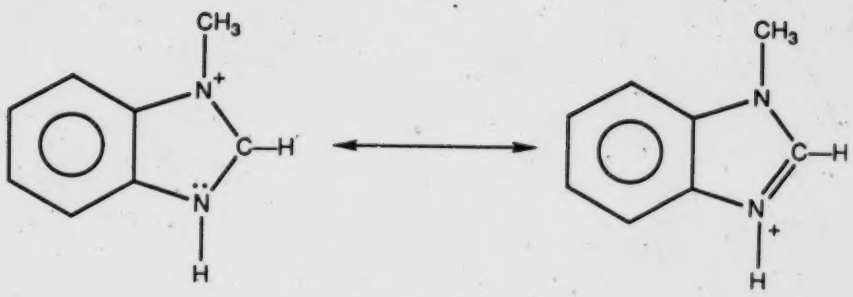
Substance	pK_a Values		
	In water	In 50% ethanol	In 5% ethanol
Benzimidazole	5.48	4.98	5.52
4(or 7)-Methyl-	5.67	5.16	—
5(or 6)-Methyl-	5.81	5.32	5.65
4,6(or 5,7)-Dimethyl-	—	5.46	—
5,6-Dimethyl-	5.98	5.48	5.99
2-Methyl-	6.19	5.77	6.10
2-Ethyl-	6.20	5.69	6.15
2-*n*-Propyl-	—	5.66	—
2-Isopropyl-	6.23	5.79	6.08
2-*tert*-Butyl-	—	5.76	—
1-Methyl-	5.57	4.88	—
1-Ethyl-	5.62	4.88	—
1-*n*-Propyl-	5.46	4.83	—
1-Isopropyl-	5.74	4.97	—
1-*n*-Butyl-	5.31	4.75	—
1-Allyl-	—	4.58	—
1-Hydroxymethyl-	5.44	4.99	—
1-(2-Hydroxyethyl)-	5.29	4.82	—
1,5-Dimethyl-	—	5.22	—
1,6-Dimethyl-	—	5.17	—
2,5(or 2,6)-Dimethyl-	—	6.03	—
1,2,5-Trimethyl-	—	6.07	—
1,5,6-Trimethyl-	—	5.45	—
2,5,6-Trimethyl-	—	6.29	6.26
2-Phenyl-	—	4.51	5.33
2-Phenyl-5,6-dimethyl-	—	5.10	—
4(or 7)-Methoxy-	—	4.98	—
5(or 6)-Methoxy-	—	5.07	5.72
5-Methoxy-1-methyl	—	5.07	—
5(or 6)-Methoxy-2-methyl-	—	5.93	—
5-Methoxy-1,2-dimethyl-	—	5.86	—
5(or 6)-Chloro-	—	3.92	—
5-Chloro-1-methyl-	—	2.88	—
6-Chloro-1-methyl-	—	3.88	—
5(or 6)-Chloro-2-methyl-	—	4.71	—
5-Chloro-1,2-dimethyl-	—	4.75	—
4,6(or 5,7)-Dichloro-	—	2.76	—
5,6-Dichloro-	—	3.26	4.74
5(or 6)-Nitro-	—	2.68	4.50
5-Nitro-1-methyl-	—	2.67	—
5(or 6)-Nitro-2-methyl-	—	3.37	—
2-Amino-	—	7.39	—
5(or 6)-Amino-	6.11	—	—

It may be seen that electron-releasing groups increase the basic strength, while electron-attracting groups exhibit the opposite effect. The influence of a given substituent varies markedly with its position on the benzimidazole ring. A methyl group in the 2-position exerts a more pronounced effect than one in the 5(or 6)- or the 4(or 7)-position. The marked effect of a 2-methyl group seems to be the result of a combination of inductive and hyperconjugative effects. Induction seems to be the dominant factor since such compounds as 2-ethyl-, 2-isopropyl-, and 2-tert-butylbenzimidazole exhibit the same basic strength as does the 2-methyl derivative. However, the ability of 2-methylbenzimidazole to condense with aldehydes is suggestive of some hyperconjugation.

Symmetry considerations may offer a plausible explanation for the observation that a methyl group in the 1-position fails to increase the basic strength of benzimidazole. In contrast to the 2-methylbenzimidazolium ion, which is highly symmetrical, the 1-methylbenzimidazolium ion receives contributions from two non-equivalent structures. The resulting loss in resonance energy may offset the electron-releasing influence of the methyl group [1].



2-methylbenzimidazolium ion

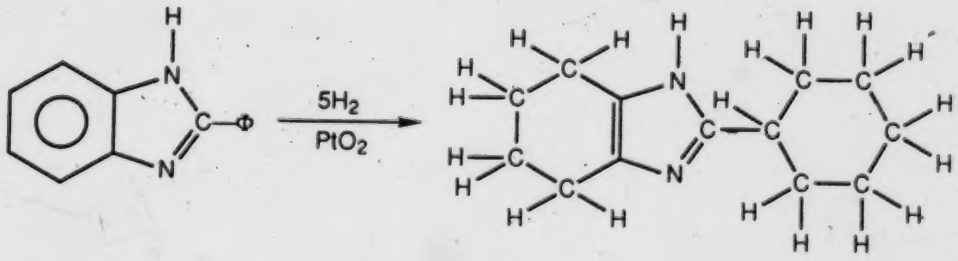


1-methylbenzimidazolium ion

5. CHEMICAL PROPERTIES

The most outstanding property of the benzimidazoles is their pronounced chemical stability. They are resistant to drastic treatment with acids and bases, and are not readily attacked by oxidizing agents. Oxidation with permanganate converts a number of methylbenzimidazoles into the corresponding benzimidazole-carboxylic acids. Drastic oxidation with potassium permanganate removes the benzene portion of the ring with the formation of 4,5-imidazoledicarboxylic acid.

Benzimidazole is unaffected by drastic conditions of hydrogenation. Hydrogenation over platinum oxide in glacial acetic acid converts 2-methyl-, 2-ethyl-, and 1,2-dimethylbenzimidazole into the corresponding tetrahydro derivatives [25]. 2-Phenylbenzimidazole under these conditions is transformed into 2-cyclohexyl-4,5,6,7-tetrahydrobenzimidazole.



6. APPLICATIONS

6.1 Applications of Benzimidazole

Benzimidazole treatment of plants increased the water efflux of plants, water influx of ozonated plants, and appeared to increase the calculated hydraulic conductivity for these fluxes. Benzimidazole prevented the immediate ozone-induced electrolyte leakage, increased water potential and decreased osmotic potential. It is proposed that benzimidazole changes some structural components of plant cell membranes [26].

It is known that benzimidazole stimulates chlorophyll formation [27], increases the number of intergrana and grana chloroplast lamellae [28] and conserves chlorophyll and proteins [29]. Benzimidazole increased the NADP and ATP content of senescing wheat leaves [30], and it was suggested that lamellar membrane permeability was decreased.

Benzimidazole increased K^+, Na^+ and Ca^{2+} uptake in excised barley roots and K^+ uptake in intact barley roots [31].

Benzimidazole is used as an anti-foggant during photographic development [32].

6.2 Applications of Substituted Benzimidazole

Benzimidazoles or their precursors have been used extensively as fungicides. The most important commercial product is methyl-1-(butyl-carbamoyl)benzimidazol-2-yl-carbamate (Benomyl) [33]. This material is a protective and eradicant fungicide with systemic activity, effective against a wide range of fungi affecting fruits, vegetables, and field crops; it is effective

against mites, primarily as an ovicide. It is also used as pre- or post-harvest sprays or dips for the control of storage rots of fruits and vegetables [3]. Other benzimidazole fungicides worthy of mention are thiabendazole, carbendazim, cypendazole, fuberidazole, and thiophanate-ethyl [34].

Benzimidazoles have also been marketed extensively as veterinary anthelmintic agents [35-38]. Notable of these are albendazole, oxfendazole, fenbendazole, cambendazole, mebendazole, oxibendazole, parbendazole, and thiabendazole [35-38].

A range of compounds based on the benzimidazole nucleus such as benomyl, thiabendazole, nocodazole, and methyl benzimidazol-2-yl carbamate are widely used anti-mitotic drugs [39]. These compounds appear to inhibit microtubule-mediated cellular functions [39]. Nocodazole is also an antineoplastic agent [3].

In experimental animals and man omeprazole, a substituted benzimidazole, has been shown to be a powerful and long-lasting inhibitor of gastric acid secretion [39-41,42], suggesting that this class of compounds is suitable for the treatment of duodenal or peptic ulcer disease.

Benzimidazole derivatives have also been found to be novel potential anticancer agents [43]. Clemizole, a substituted benzimidazole, is an antihistamine [3] and Diabazole acts as a vasodilator spasmolytic hypotensive [3]. Benperidol, pimozide, and droperidol are all substituted benzimidazoles used as psychopharmacological agents [3]. Benzitramide is an analgesic and clemizole penicillin is used as a bactericide [3].

Benzimidazole derivatives have also been evaluated for use in the following areas: corrosion inhibitors for copper [44-48], brass [46,49,50], and

aluminum [51]; photosensitive compounds for use in photothermography [52,53] and for the preparation of silver-free photographic films [54,55]; and polymer additives as stabilizing [56] and shrinking agents [57], as fluorescent brighteners [58], and as merocyanine derivatives for use as sensitizing dyes [59-61].

Domperidone is a new benzimidazole antiemetic used for the treatment of postoperative nausea and vomiting [44].

7. TITRATIONS IN NONAQUEOUS SOLVENTS

In general, the acid-base behavior of any solute dissolved in a given solvent will depend on the interplay of at least three factors. These are the acid-base properties of the solvent relative to the solute, the autoprotolysis constant of the solvent, and the dielectric constant of the solvent [62]. These factors are discussed in the following sections. The low solubility and weak acid-base character of the benzimidazoles make their protonation and titration behavior in solvents other than water of considerable analytical interest.

7.1 Classification of Solvents

An amphiprotic solvent is one capable of acting as either a Bronsted-Lowry acid or base. Amphiprotic solvents undergo self-dissociation or autoprotolysis, according to

$$2SH \rightleftharpoons SH_2^+ + S^-$$

Examples of amphiprotic solvents include water, acetic acid, ammonia, ethylenediamine, and alcohols like methanol and ethanol [63]:

$$2H_2O \rightleftharpoons H_3O^+ + OH^-$$

$$2HOAc \rightleftharpoons H_2OAc^+ + OAc^-$$

$$2NH_3 \rightleftharpoons NH_4^+ + NH_2^-$$

$$2H_2NCH_2CH_2NH_2 \rightleftharpoons H_2NCH_2CH_2NH_3^+ + H_2NCH_2CH_2NH^-$$

$$2CH_3OH \rightleftharpoons CH_3OH_2^+ + CH_3O^-$$

An aprotic solvent is one which has little or no acidic or basic character and also little or no tendency to undergo self-dissociation. Aprotic solvents having slight acid-base properties include dimethylsulfoxide $(CH_3)_2SO$, acetonitrile CH_3CN, and dimethylformamide $(CH_3)_2NCHO$. Those having no appreciable acid-base properties include carbon tetrachloride (CCl_4), benzene (C_6H_6), and hexane (C_6H_{14}); these are often termed inert because they show so little tendency to undergo reaction with substances dissolved in them.

A few solvents, including pyridine, the ethers, and several ketones, do not fit readily into either the amphiprotic or aprotic classes. They possess definite basic properties, being able to accept protons on basic nitrogen or oxygen atoms, but their acid properties are negligible, and so they are often useful solvents for the titration of weak acids [63].

7.2 Leveling Effect and Differentiating Ability of a Solvent

When acids or bases are dissolved in amphiprotic solvents, partial Brönsted neutralization (protolysis) occurs owing to the establishment of the following equilibria:

$$AH + SH \rightleftharpoons A^- + SH_2^+$$

$$B + SH \rightleftharpoons BH^+ + S^-$$

(SH = solvent; AH = acid; B = base)

If equilibrium lies well to the right, *i.e.* if ionization is favored, a special situation arises which Hantzsch [64] referred to as leveling. In this case the original strong acids or bases are largely replaced by lyonium and lyate ions, which are the strongest acids and bases that can exist in the solvent in question. The difference in strengths originally present in a mixture of strong acids or bases is eliminated *i.e.* leveled. The resulting solutions may be referred to as salt solutions [65]. An example of leveling known in practice is that of aqueous solutions of strong mineral acids. Thus on considering the acid strengths of perchloric acid and hydrochloric acid in water, the following acid base equilibria are involved:

$$HClO_4 + H_2O \rightleftharpoons ClO_4^- + H_3O^+$$

$$HCl + H_2O \rightleftharpoons Cl^- + H_3O^+$$

Because $HClO_4$ and HCl are both much stronger acids than the hydronium ion H_3O^+ or, put another way, because water is a stronger base

than either ClO_4^- or Cl^-, the position of equilibrium in each case lies so far to the right that it is impossible experimentally to distinguish any difference between the two equilibrium positions. Inasmuch as the strengths of perchloric and hydrochloric acids appear to be identical in water, we speak of water as exerting a leveling effect on these two acids and the acid strengths of $HClO_4$ and HCl are both reduced to that of H_3O^+.

If the same acids, $HClO_4$ and HCl, are compared in glacial acetic acid as solvent, the pertinent acid-base reactions are

$$HCl + CH_3COOH \rightleftharpoons Cl^- + CH_3COOH_2^+$$

and

$$HClO_4 + CH_3COOH \rightleftharpoons ClO_4^- + CH_3COOH_2^+$$

Glacial acetic acid is a much weaker base than water and thus the protonated acetic acid molecule ($CH_3COOH_2^+$) is a stronger acid than the hydronium ion (H_3O^+). Therefore neither of these acid-base reactions proceeds as far to the right in acetic acid as in water. However, the superior acid strength of perchloric acid is confirmed by the fact that its reaction with the glacial acetic acid solvent attains a greater degree of completion than the reaction of hydrochloric acid with the solvent. Hence, glacial acetic acid possesses the capability to differentiate the acid strengths of $HClO_4$ and HCl and is called a differentiating solvent.

Also, a strong basic solvent such as liquid ammonia would fail to differentiate a mineral acid from acetic acid because the reactions

$$HClO_4 + NH_3 \rightleftharpoons ClO_4^- + NH_4^+$$

and

$$CH_3COOH + NH_3 \rightleftharpoons CH_3COO^- + NH_4^+$$

would both proceed virtually to completion because of the base strength of NH_3.

7.3 Autoprotolysis Constant

Another factor which affects the differentiating ability of a given solvent is its autoprotolysis constant. For an amphiprotic solvent, SH, the general form of the autoprotolysis reaction is

$$SH + SH \rightleftharpoons SH_2^+ + S^-$$

and the corresponding equilibrium expression is

$$K = \frac{a_{SH_2^+} a_{S^-}}{a_{SH}^2}$$

By convention the activity of the pure solvent (SH) is taken to be unity and for the majority of solvents the extent of autoprotolysis is quite small, so that activities of ions can be replaced by their analytical concentrations. Hence, the simplified form for the autoprotolysis equilibrium expression is

$$K_S = [SH_2^+][S^-]$$

The useful pH range for a solvent increases as the autoprotolysis constant decreases. In other words, the smaller the autoprotolysis constant, the greater is the range of acid or base strengths which can exist in a solvent and the greater is the likelihood that it will be a differentiating solvent. Formic acid, with an autoprotolysis constant of 6.3×10^{-7} ($pK_S = 6.2$), is a poor differentiating solvent because only a very narrow range of acid strengths can exist in it. Thus, the differentiating ability of a particular solvent must be carefully assessed in terms of both its autoprotolysis constant and its acid-base properties relative to the solutes dissolved in it. Water, with an autoprotolysis constant of 1.00×10^{-14} at 25°C, cannot differentiate the strong mineral acids because it is a relatively basic solvent. On the other hand, glacial acetic acid has an autoprotolysis constant of similar magnitude (3.2×10^{-15}), but the mineral acids are differentiated in it because of the acidic character of glacial acetic acid [62].

7.4 Effect of the Dielectric Constant

Another factor to be reckoned with in nonaqueous acid-base titrimetry is that, compared to water, most other solvents have low dielectric constants. The reaction of an uncharged solute acid BH with a solvent SH can be described in terms of two discrete processes — ionization and dissociation:

$$BH + SH \underset{\text{ionization step}}{\rightleftharpoons} \{B^-HSH^+\} \underset{\text{dissociation step}}{\rightleftharpoons} B^- + HSH^+$$

In the ionization step, a proton is transferred from the solute acid BH to the solvent SH, giving rise to the ion pair B^-HSH^+. There is a definite separation of

charges in such an ion pair, although the individual B^- and HSH^+ ions are very close to each other. Dissociation occurs when additional solvent molecules attack the ion pair and separate it completely into solvated B^- and HSH^+ ions. According to Coulomb's law, the force of attraction between two oppositely charged ions is inversely proportional to the dielectric constant of the medium (solvent) in which the ions exist. For solvents of high dielectric constant such as water (D = 78.5 at 25°C), the force of attraction between the ions of an ion pair is relatively small and the dissociation step will be virtually complete. However, for solvents having low dielectric constants such as ethanol (D = 24.3), glacial acetic acid (D = 6.1), and methyl isobutyl ketone (D = 13.1), there is considerable ion pairing as well as formation of larger ion aggregates.

One would expect the acidity of a positively charged solute of the type BH^+ to be largely unaffected by variations in the dielectric constant of the solvent because the transfer of a proton from BH^+ to SH does not produce an ion pair

$$BH^+ + SH \underset{\text{ionization step}}{\rightleftharpoons} \{BHSH^+\} \underset{\text{dissociation step}}{\rightleftharpoons} B + HSH^+$$

In the absence of ion pairs, neither the ionization step nor the dissociation step involves the separation of charges. This line of reasoning might be expected to apply in the case of species such as ammonium ion (NH_4^+) or pyridinium ion ($C_5H_5NH^+$). However the NH_4^+ species, for example, must be added to the solvent in the form of an ammonium salt, the anion of which would undoubtedly form ion pairs with NH_4^+ and thereby influence its acid strength.

A low dielectric constant for a given solvent SH has a pronounced effect on the autoprotolysis constant K_S of that solvent. As shown by the following reaction scheme, the detailed process of autoprotolysis should include an ion-pair intermediate

$$SH + SH \underset{\text{ionization step}}{\rightleftharpoons} \{S^-HSH^+\} \underset{\text{dissociation step}}{\rightleftharpoons} S^- + HSH^+$$

so that the autoprotolysis constant is the product of an ionization constant and a dissociation constant:

$$K_S = [HSH^+][S^-] = K_{ioniz}K_{diss}$$

If the magnitude of the dissociation constant K_{diss} is small because the dielectric constant of the solvent is low, the autoprotolysis constant K_S is likely to be small. This effect seems to be operative for glacial acetic acid which has a surprisingly low dielectric constant of 6.1 and an autoprotolysis constant of 3.5×10^{-15}. In sharp contrast to glacial acetic acid is anhydrous formic acid. Although formic acid is chemically very similar to acetic acid, its autoprotolysis constant is 6.3×10^{-7}. Such a relatively large autoprotolysis constant is partly explicable on the basis of the high dielectric constant of 58.5 for formic acid which promotes the dissociation of ion pairs of the type $HCOO^-HCOOH_2^+$. Water is a unique solvent because of its unusually high dielectric constant and its relatively small autoprotolysis constant [62].

8. APPLICATIONS OF NONAQUEOUS ACID-BASE TITRATIONS

A wide range of organic compounds, such as alcohols, esters, anilides, carbamates, acetophenones, and lactams, can be titrated as very weak acids in tetrahydrofuran with lithium [1,1,1-trimethyl-N-(trimethylsilyl)]silanamide [66]. End points can be obtained either potentiometrically with a platinum indicating electrode or visually with N-phenyl-p-aminoazobenzene as indicator. The titrant is stable at least a week under a nitrogen atmosphere. Organic acids, phenols, and aromatic nitro compounds can be determined by titration with diphenylguanidine in 2-methoxyethanol [67]. End points can be obtained conductometrically and are comparable in precision and accuracy to conventional nonaqueous titrations. The end point with nitrobenzene is as sharp as with phenol; no explanation for this behavior is available, but donor-acceptor complex formation seems likely. The weak organic base pholcodine can be titrated conductometrically with tungstosilicic acid in acetic and or in aqueous ethanol. The titration curves are more analytically suitable than those obtained with perchloric acid [68].

A study of bases in acetic acid, and their differential titration, has been made [69]. Differentiation potentiometric titration is feasible if the difference in the pK_b values is four or more. The color changes of indicators in nonaqueous systems have been considered, and the indicator transitions compared with theoretical titration curves [70]. Organic amine hydrochlorides have been determined by conversion to the acetates by passage through a strong base anion exchanger in acetic acid as solvent [71]; the acetate salt is then titrated with hydrochloric acid in acetic acid.

The pK_a values for 13 hydroxyanthraquinones are linearly related to the values in acetone, dimethylformamide, or dimethylsulfoxide [72]. Dimethylsulfoxide is the most satisfactory solvent of this group for analytical applications. Of four methods tested for the determination of penicillamine in a drug formulation, titration with perchloric acid is generally preferred, although somewhat less precise than titration with mercury(II) acetate [73]. Mixtures of polybasic benzenecarboxylic acids can be separated into fractions by dissolution in acetone, titration to the corresponding salts with sodium hydroxide in ethanol, and then stepwise back-titration with hydrochloric acid in acetone to intermediate pH values, each time stopping to extract the neutral acids present [74]. Hydrochloride salts of peptides and amino acids can be titrated after addition of mercury(II) acetate, with perchloric acid in nitromethane as solvent. This solvent suppresses interference from sulfur-containing groups by keeping them from reacting with mercury(II) [75].

Binary mixtures of methylisobutyl ketone with methanol, dioxane, benzene, or acetic acid give smooth titration curves with sharp inflections when used as solvents for the titration of organic bases with perchloric acid in methylisobutyl ketone [76]. Nitroaminobenzanilides can be titrated as bases in glacial acetic acid with perchloric acid, or as acids in dimethylformamide, N-methylpyrrolidine, or acetone with tetraethylammonium hydroxide in benzene-ethanol [77].

The potassium alcoholates of the C_3 to C_5 alcohols have been investigated as titrants for weak acids [78]. Solutions of potassium butoxide and potassium-2-propoxide in 1:5 mixtures of the corresponding alcohols with

toluene are less sensitive to atmospheric carbon dioxide than solutions of potassium methoxide.

Oxygen in steel can be measured by oxidation of the CO extracted from the steel sample with copper(II) oxide, absorption of the resulting CO_2 in 5 vol% monoethanolamine in dimethylformamide, and titration of the CO_2 with tetrabutylammonium hydroxide in benzene-methanol [79]. Sucrose has been found to be a suitable standard reference material for the system. Mixtures of chlorinated acetic acids can be titrated potentiometrically in 4:1 acetone-acetonitrile with potassium-2-propoxide in 2-propanol as titrant if phthalic acid is present as a differentiating electrolyte [80]. Tetrahydrofuran is not suitable as a solvent for the differential potentiometric titration of mixtures of nitrophenols with tetrabutylammonium hydroxide in benzene-methanol as titrant, but in 1:1 mixtures with acetone, dimethylsulfoxide, dimethylformamide, or methanol the differentiating properties are superior to any of the solvents individually [81]. The free acid and anhydride content of samples of aliphatic or aromatic anhydrides can be obtained by dissolution in acetone and conductometric titration with sodium methoxide in methanol [82]. A procedure for the determination of basic organomagnesium and organolithium reagents is based on deprotonation of N-phenyl-1-naphthylamine to form the highly colored magnesium or lithium derivative, which is then titrated with 2-butanol in xylene [83]. Boric acid can be titrated after conversion to tetrafluoroboric acid with sodium or potassium acetate in glacial acetic acid [84]. N,N-Diethylaniline or pyridine can also be used as titrants; end points can be obtained by potentiometry or conductometry. Some applications of acid-base titrimetry in nonaqueous solvents are given in Table 2.

Table 2. Some Substances Determined by Acid-Base Titrations in Nonaqueous Solvents (Adapted from Ref. 85).

Substance	Titrant	Solvent	End-point Method
substituted phenylbenzimidazoles	$HClO_4$ in dioxane	Me_2CO	pot., glass ind. electrode
diazepam, napoton, nitrazepam	$HClO_4$ in HOAc	HOAc	pot. glass ind. electrode
aminophenazone, caffeine, Na silicylate	$HClO_4$ in dioxane	$(EtCO)_2O$-dioxane	pot. glass ind. electrode
thiamine-HCl	$HClO_4$ in HOAc	HOAc-Ac_2O	pot., glass ind. electrode
organic sulfides	$HClO_4$ in HOAc	HOAc or Ac_2O, $Hg(OAc)_2$	pot., glass ind. electrode
pyrazole and derivatives	$HClO_4$ in HOAc	HOAc, $Hg(OAc)_2$	pot., glass ind. electrode
meclozine•2HCl	$HClO_4$ in HOAc	HOAc	conductance
berbamine	$HClO_4$ in HOAc	HOAc, H_2O	crystal violet ind.
trimethoprim	$HClO_4$ in HOAc	$CHCl_3$	crystal violet ind.
oxaminiquine	$HClO_4$ in HOAc	HOAc	quanaldine red ind.
pholcodine	$HClO_4$ in HOAc	HOAc	conductance
trimethoprimsulfamethoxazole mixtures	$HClO_4$ in HOAc	Me_2CO-HOAc	pot., glass ind. electrode
N-arylhydroxamic acids	Bu_4NOH in CH_6H_6MeOH	DMF	*o*-NO_2 aniline ind.
phenobarbitol-papaverine•HCl mixtures	Et_4NOH in EtOH	DMSO	thymol blue ind.
5,5-dimethylhydantoin	Et_4NOH in C_6H_6MeOH	DMF-C_6H_6	pot., glass ind. electrode
carbazoles, nitrocarbazoles	Et_4NOH in C_6H_6MeOH	DMSO, DMF, MeCN, or Me_2CO	pot., glass ind. electrode
1,2,3-benzotriazole-N-hydroxy-1,2,3-benzotriazole	KOH in 2-PrOH	2-PrOH-C_6H_6	pot., glass ind. electrode
cinnamic acid-chalcone mixtures	KOH in 2-PrOH	Me_2CO	pot., glass ind. electrode
organic acids and anhydrides	KOH in EtOH	PrOH-C_6H_{14}-H_2O	pot., glass ind. electrode
L-carnotine•HCl	KOH in EtOH	EtOH	pot., glass ind. electrode
ampicillin, tetracycline•HCl, doxycycline•HCl	NaOH in MeOH	$(Me_2N)_2CO$	pot., glass ind. electrode or thymol blue ind.
nicotinic acid	NaOH in MeOH	MeOH-C_6H_6	resazurin ind.
ammonium perchlorate-perchloric acid mixtures	R_4NOH or KOH in EtOH or 2-PrOH	2-PrOH or Me_2CO	pot., glass ind. electrode, 2 end points

CHAPTER II

WEIGHT TITRATIONS OF BENZIMIDAZOLE AND SUBSTITUTED BENZIMIDAZOLES IN A NONAQUEOUS MEDIUM

1. INTRODUCTION

A weight, or gravimetric titration is one in which the weight rather than the volume of titrant is measured. The advantages are that (a) weight can be determined more accurately and precisely than volume; (b) procedures necessitated by use of volumetric ware (burets, pipets and flasks), with the necessity for calibration and removing traces of grease for efficient drainage, are not required; (c) small amounts of titrant and sample do not cause loss of precision or accuray when reagents are expensive or samples are limited; and (d) errors in volume measurement due to expansion or contraction of solvent with temperature are avoided [63].

The technique is particularly applicable in photometric titrations, where small volumes are more convenient and give greater precision in that they permit titration directly in a spectrophotometric cell without removal of the cell from the instrument.

Despite these advantages, weight titrations have not been popular, principally because several weighings may be required, a tedious process with old-style balances. But with the advent of top-loading balances capable of weighing quickly and accurately to within a milligram or better, weight titrations are now feasible, and often may be preferable to volumetric methods. An application for which weight titrations are particularly recommended is that

where the titrant is dissolved in an organic solvent. Acetic acid, like most organic liquids, has a cubic coefficient of thermal expansion almost five times that of water; the change in volume is about 1 ppt/°C. Thus small changes in temperature affect the volume of titrant markedly [63].

In this chapter the weak base benzimidazole and several substituted benzimidazoles are determined by weight titration with a strong acid, perchloric acid, in the organic solvent acetic acid. Acetic acid provides both solubility and the requisite acid-base properties. The perchloric acid titrant is also dissolved in glacial acetic acid and is standardized against primary-standard potassium acid phthalate. The indicators used are α-naphtholbenzein and crystal violet. The titrant is delivered from a 10-mL syringe with a stainless-steel needle. The syringe serves as a convenient vessel for weighing and delivering the titrant and reduces losses from evaporation.

2. EXPERIMENTAL

2.1 Chemicals

Benzimidazole, 2-phenylbenzimidazole, 5-nitrobenzimidazole, 2-methylbenzimidazole, and 5,6-dimethylbenzimidazole (Aldrich Chemical Company) were recrystallized at least three times from 6:1 (v/v) methanol:water. Purity was checked by melting point determination as shown in Table 3 and elemental analysis. A further check was provided by titration with perchloric acid in glacial acetic acid as solvent. All other chemicals were reagent grade or better and were used as received.

Table 3. Melting Points of Benzimidazole and Substituted Benzimidazoles.

	m.p., °C (Found)	m.p., °C (Literature value)
Benzimidazole	170	170-172[a]
2-Phenylbenzimidazole	291	290[a]
5-Nitrobenzimidazole	206-208	204-206[b]
2-Methylbenzimidazole	175-177	178.5[c]
5,6-Dimethylbenzimidazole	203-204	204-205[a]

[a]Data from Ref. 86.

[b]Data from Ref. 87.

[c]Data from Ref. 24.

Crystal violet indicator was prepared by dissolving 0.2 g of crystal violet (National Aniline Division, Allied Chemical and Dye Corp.) in 100 mL of glacial acetic acid.

A 0.05% α-naphtholbenzein solution was prepared by dissolving 0.5 g α-naphtholbenzein (Eastman Kodak Co.) in 1 L of isopropanol.

A 0.1 *M* solution of perchloric acid in glacial acetic acid was used as titrant. It was prepared as follows: 0.85 mL of 70 to 72% perchloric acid (Fisher Scientific Co.) was measured with a Mohr pipet into 10 to 15 mL of reagent grade acetic acid. About 2 mL of acetic anhydride was added and the solution allowed to stand for about 30 min. The solution was then diluted to 100 mL with glacial acetic acid and stored in a well-stoppered glass container. The exclusion or removal of water from the perchloric acid titrant is desirable to prevent leveling effects and improve the sharpness of titration curves. A stoichiometric quantity of acetic anhydride was added to consume water by the reaction

$$(CH_3CO)_2O + H_2O \rightarrow 2CH_3COOH$$

2.2 Procedure for Standardization of Perchloric Acid Titrant

The perchloric acid was standardized using solutions of potassium acid phthalate (KHP). These solutions were prepared by weighing, to the nearest 0.1 mg, samples of approximately 0.15 g of primary-standard potassium acid phthalate into 200-mL conical flasks. About 20 mL of glacial acetic acid was added to each flask and the flasks then swirled to dissolve. Two or three drops of indicator were added to each flask. Two indicators were used, α-naphtholbenzein and crystal violet. Each of the solutions was then titrated using

perchloric acid titrant, delivered from a plastic, disposable 10-mL syringe (Fisher Scientific Co.), to a color change of yellow to green for α-naphtholbenzein and violet to blue for crystal violet.

The amount of perchloric acid titrant used for the titration was determined by weighing the syringe before and after the titration on a top-loading balance to ±1 mg.

2.3 Procedure for the Titration of Benzimidazoles with Plastic, Disposable Syringe

About 0.3 g of sample (benzimidazole or derivatives) was weighed to the nearest 0.1 mg and transferred into a clean, dry stoppered 50-mL volumetric flask previously weighed on a top-loading balance to the nearest mg. The sample was diluted to about 50 mL with glacial acetic acid and the flask stoppered and reweighed.

About 10 to 12 g of the sample solution was weighed (±1 mg) into a 200-mL conical flask and titrated with perchloric acid titrant delivered from a plastic, disposable 10-mL syringe and using α-naphtholbenzein and crystal violet indicators as for the standards. For α-naphtholbenzein the color change was from yellow to olive green and for the crystal violet indicator it was from violet to blue.

Again, the amount of perchloric acid titrant used for the titration was determined by weighing the syringe before and after each titration on a top-loading balance to the nearest milligram.

3. RESULTS AND DISCUSSION

3.1 Standardization of Perchloric Acid Titrant

Perchloric acid solutions in glacial acetic acid are usually standardized against potassium acid phthalate (KHP). In this titration the KHP acts as a base, the HP^- ion accepting a proton from the acid $CH_3COOH_2^+ClO_4^-$ to form H_2P:

This reaction is driven to the right in part by the strength of the titrant acid and in part by the tendency of HP^- to accept a proton in a solvent system such as glacial acetic acid [63].

The weight molarity of the perchloric acid is calculated by

$$\text{wt. molarity } HClO_4 \text{ (mmoles/g)} = \frac{(\text{g KHP})(10^3 \text{ mmoles/mole})}{(\text{mol wt. KHP})(\text{wt. titrant, g})}$$

Results of the manual standardization titrations using indicator end point detection gave weight molarities for the perchloric acid of 0.0914 ± 0.0014 for eight (8) titrations using α-naphtholbenzein as indicator, and 0.0934 ± 0.0024 for five (5) titrations using crystal violet as indicator. The difference between the two is not significant at the 95% confidence level by the student t test as shown. The pooled s, denoted s_p is given by

$$s_p = \left[\frac{(n_1 - 1)(s_1^2) + (n_2 - 1)(s_2^2)}{(n_1 - 1) + (n_2 - 1)}\right]^{0.5}$$

where n_1 and n_2 are the number of measurements for the two sets of data and S_1 and S_2 are the standard deviations for the two sets of data. Hence

$$s_p = \sqrt{\frac{7(0.0014)^2 + 4(0.0024)^2}{7 + 4}} = 0.00214$$

The value t is determined from the expression

$$t = \frac{|\bar{x}_1 - \bar{x}_2|}{s_p}\left[\frac{n_1 n_2}{n_1 + n_2}\right]^{0.5}$$

where $\bar{x}_1$ and $\bar{x}_2$ are the means for the two data sets. Therefore the t value is given by

$$t = \frac{0.002}{0.002142}\left[\frac{(8)(5)}{8 + 5}\right]^{1/2} = 1.638$$

For eleven (11) degrees of freedom the t value at 95% confidence level, *i.e.* t_{95} from tables [63] is 2.23 which is greater than the value calculated above (1.638). Therefore the two weight molarity values may be deemed not significantly different at the chosen 95% level of confidence and the two indicators may be considered to give the same answer within experimental error.

3.2 Results Obtained With Weight Titrations of Raw and Recrystallized Compounds

This section discusses the results obtained when the titrations of raw and recrystallized compounds were performed using plastic, disposable syringes as described in Section 2.3.

The percentage purity of each compound was determined as follows:

$$\% \text{ purity} = \frac{(\text{Wt. molarity } HClO_4)(a)(b)(\text{Mol. wt. comp'd.})(100)}{(c)(d)}$$

where a = total weight of 50-mL sample solution, b = weight of perchloric acid titrant, c = weight of sample solution aliquot used for titration, and d = weight of solid taken for preparation of sample solution.

The results are summarized in Table 4. These results indicate that the purity of the benzimidazole compounds is somewhat enhanced after recrystallization. This is evidenced by the percentage purity values of the re-crystallized samples being higher than those of the raw samples.

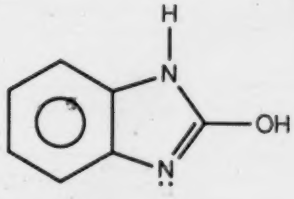
Furthermore, percentage purity values of recrystallized samples obtained using α-naphtholbenzein tend to be higher than those of the crystal violet indicator, and in most cases, the standard deviation is smaller using α-naphtholbenzein as indicator. This probably indicates a sharper end point is achieved using the α-naphtholbenzein.

It can also be seen that the precision is consistently better for titrations of recrystallized material when using α-naphtholbenzein as indicator, but is not significantly different for the titrations using crystal violet as indicator. Also, the average percentage values for crystal violet were lower in almost all the

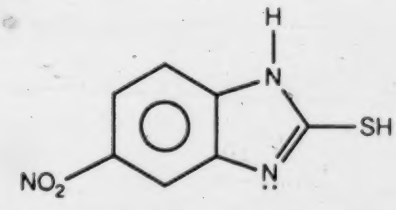
titrations. It was therefore decided to perform some potentiometric pH titrations with indicator present to determine whether the crystal violet was giving too early an end point. These titrations are described in the next chapter.

Comparison of the percentage purity experimentally determined here with values reported by the manufacturers of the compounds, show close agreement, lending support to the conclusion that the titration method is sensitive and accurate enough for the determination of benzimidazole compounds in nonaqueous medium.

An attempt was made to carry out similar titrations for 2-hydroxybenzimidazole and 2-mercapto-5-nitrobenzimidazole, but in each case the indicator changed color on addition of only a few drops of the titrant. As a result no reasonable quantitative information was obtained. From the structures of 2-hydroxybenzimidazole and 2-mercapto-5-nitrobenzimidazole it may be that the basic nitrogen is protonated by the hydrogens of the hydroxyl and mercapto groups to form a zwitterion in solution with only weakly basic properties. This could account for the sudden change of the indicator color observed in the attempted titrations of these two compounds.



2-hydroxybenzimidazole
(F.W. 134.14)



2-mercapto-5-nitrobenzimidazole
(F.W. 195.20)

Table 4. Percentage Purity of Substituted Benzimidazoles by Weight Titration Using α-Naphtholbenzein and Crystal Violet as Indicators.*

Compound	% Purity	
	α-Naphtholbenzein	Crystal Violet
Benzimidazole		
raw	97.46 ± 0.74 (8)	97.29 ± 0.75 (4)
recrystallized	99.02 ± 0.61 (8)	97.95 ± 0.89 (8)
2-Phenylbenzimidazole		
raw	98.24 ± 0.64 (8)	97.49 ± 0.94 (4)
recrystallized	99.13 ± 0.14 (5)	98.16 ± 0.86 (8)
2-Methylbenzimidazole		
raw	97.87 ± 0.93 (8)	97.96 ± 0.44 (8)
recrystallized	99.01 ± 0.68 (8)	98.95 ± 0.33 (8)
5-Nitrobenzimidazole		
raw	98.30 ± 1.19 (8)	97.05 ± 0.80 (4)
recrystallized	99.11 ± 0.43 (8)	97.54 ± 0.94 (8)
5,6-Dimethylbenzimidazole		
raw	98.93 ± 0.56 (4)	98.53 ± 0.65 (4)
recrystallized	99.50 ± 0.42 (8)	99.08 ± 0.52 (8)

*Uncertainties are ± one standard deviation. Number of titrations for each data set is given in parentheses.

4. CONCLUSIONS

The determination of the benzimidazoles in acetic acid by weight titrations using perchloric acid as titrant has been possible with the two indicators, α-naphtholbenzein and crystal violet.

At the 95% confidence level these two indicators have been found not significantly different and therefore may be considered to give the same results within experimental error. However the α-naphtholbenzein gave results with better precision which suggests that it gives sharper end points. This was confirmed visually. Therefore α-naphtholbenzein is the preferred indicator for weight titrations of benzimidazoles in acetic acid using perchloric acid as titrant.

The results also show greater percentage purity values for the recrystallized samples but at the 95% confidence level they are not significantly different from the values obtained with the raw samples. However, titrations of recrystallized samples yield relatively better precision than do raw samples using both indicators.

CHAPTER III
AUTOMATIC POTENTIOMETRIC TITRATIONS OF BENZIMIDAZOLES IN NONAQUEOUS MEDIUM

1. INTRODUCTION

In a potentiometric titration an indicator electrode which reacts to changes in concentrations of the compound to be determined and a reference electrode having a fixed and reproducible potential are immersed in the sample solution. Variations in the potential of the indicator electrode (or a quantity correlated to it by a linear equation, like pH) with respect to the reference electrode as titrant is added allow the progress of the titration to be followed [62]. During an automatic potentiometric technique, such a titration is followed by the plotting of electrode potential (or pH) *versus* the volume (or weight) of the titrant dispensed and this titration curve is then recorded [88].

The use of automatic titrators has numerous advantages. The most important of these are savings in labor costs and time, the reduction of scales, and increased precision, achieved mainly by the application of precision microburets, and finally, a recorded titration curve can be attended to later and may be filed away for further reference [88]. Compared to other methods for the location of equivalence points, the technique of potentiometric pH titrimetry offers a number of advantages. It is applicable to systems which are so brightly colored that visual methods of end-point detection are useless, and it is especially valuable when no internal chemical indicator is available. Moreover, it eliminates subjective decisions concerning color changes of end-point indicators as well as the need for indicator blank corrections [62].

In this chapter, potentiometric pH titrations of all the five benzimidazoles studied in Chapter II were carried out in a nonaqueous medium of glacial acetic acid. The equivalence points of the titration were determined using the inverse-derivative plot method and the values obtained were used to determine the percentage purity of the five benzimidazoles. These values are then compared to those obtained in the manual titrations using the syringe.

2. EXPERIMENTAL

2.1 Apparatus

The pH values were measured using a Fisher-Accumet (Model 825 MP) pH meter. A modular automatic weight titrator was used. This system consists of a Mettler AE 160 balance (Mettler Instrument Corp., Princeton, NJ) having a range of 162 g and a readability of 0.1 mg with associated option 011 data output unit (CL/RS 232C unidirectional), a Fisher Accumet 825 MP pH meter, and an Apple II+ microcomputer. A schematic outline of the system is shown in Figure 1.

2.2 Procedure for the Titration of Benzimidazoles with a Microcomputer-Controlled Automatic Weight Titrator

About 0.3 g of sample (benzimidazole or derivatives) was weighed to the nearest 0.1 mg and transferred into a clean, dry, stoppered 50-mL volumetric flask previously weighed on a top-loading balance. The sample was diluted to 50 mL with glacial acetic acid and the flask stoppered and reweighed.

About 20 mL of the sample solution was placed in a 50-mL beaker and 2-3 drops of indicator and a magnetic stirring bar were added. The sample beaker

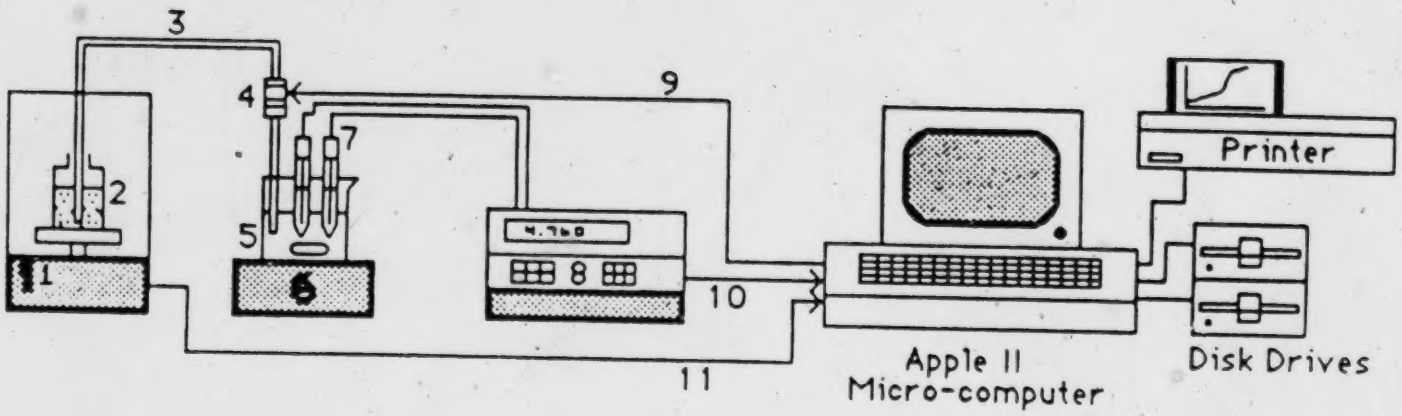


Figure 1. Schematic diagram of gravimetric titrator controlled by a microcomputer: (1) analytical balance, (2) titrant on balance pan, (3) delivery tube (Teflon), (4) solenoid valve, (5) titration vessel, (6) magnetic stirrer, (7) glass pH and calomel reference electrode pair, (8) pH meter, (9) valve controller line from Apple II game port, (10) data output line from pH meter to Apple II, and (11) data output line from balance to Apple II microcomputer. (From Chem 312 Laboratory Manual, W.E. Harris and B. Kratochvil, University of Alberta, 1988.)

was then placed on the stirrer and the pH and reference electrodes were inserted into the sample solution. Because conventional aqueous reference electrodes introduce water into the solvent, which weakens the titrant acid strength, the aqueous KCl filling solution was replaced as described by Kolthoff and Bruckenstein [89]. The procedure is detailed in Section 2.3. The titrant delivery tip was immersed in the solution and the stirrer turned on. The titration then proceeded automatically with the aid of a computer program.

2.3 Preparation of Reference Electrode for Use in Acetic Acid Solution

All compounds and reagents were analytical grade or better. An aliquot of acetic acid was saturated with sodium chloride and sodium perchlorate such that some crystals of both remained in contact with the solution. The aqueous saturated calomel solution in a Fisher reference calomel electrode was removed by siphoning through a small plastic tube, and the electrode interior was washed several times with portions of the prepared solution. Then the electrode was refilled with the prepared acetic acid solution saturated in sodium chloride and sodium perchlorate.

The reference electrode thus prepared can be represented as:

$$Hg|Hg_2Cl_2|NaCl,\ NaClO_4 \text{ saturated with both in acetic acid}|...$$

The solubility of sodium chloride in anhydrous acetic acid at 25°C is only 0.0125 molar and the much more soluble sodium perchlorate is added to minimize the liquid-junction potential and to act as salt bridge.

The acetic acid reference electrode was always kept in a portion of the prepared reference solution between titrations to maintain reproducibility.

The pH meter was calibrated using an aqueous buffer of pH 4. Following the buffer adjustment in the aqueous buffer, the glass and reference electrodes were soaked in the nonaqueous solvent (acetic acid) for 20 minutes before being used for the nonaqueous pH determinations. Between successive measurements, the electrodes were rinsed with acetic acid. The glass indicator electrode was stored in acetic acid and was soaked periodically in water to prevent nonaqueous dehydration of the glass bulb which can cause readings to drift.

3. RESULTS AND DISCUSSION

3.1 End Point Determination in Nonaqueous Potentiometric pH Titrations

Test solutions of the benzimidazoles, prepared in glacial acetic acid as described in Section 2.2, were titrated with 0.1 *M* perchloric acid in acetic acid.

Several types of standard reference half-cells have been used in acetic acid solutions. For the early studies, an aqueous calomel electrode was used and was joined to the acetic acid system by means of a saturated solution of lithium chloride [90-93]. Later, half-cells involving only acetic acid were employed. A version of the calomel electrode for use in acetic acid, described by Kolthoff and Bruckenstein [89], was prepared as outlined in Chapter 3, Section 2.3 and used in this work. This electrode was found to be quite satisfactory and reproducible for these potentiometric titrations and sharp equivalence points were detected (see Figures 2 and 3).]The equivalence

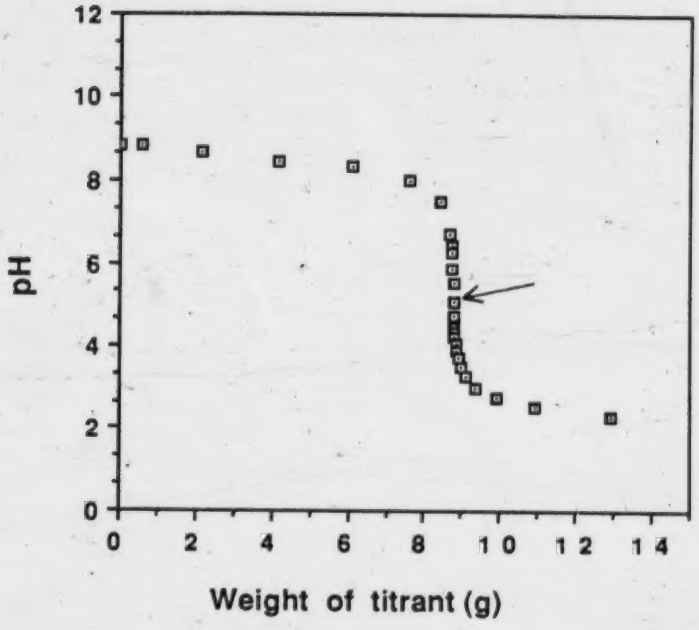


Figure 2. Titration curve of benzimidazole in glacial acetic acid with perchloric acid in glacial acetic acid. pH values are relative values. True pH = (observed pH on axis - 7). Arrow indicates point at which α-naphtholbenzein changed color.

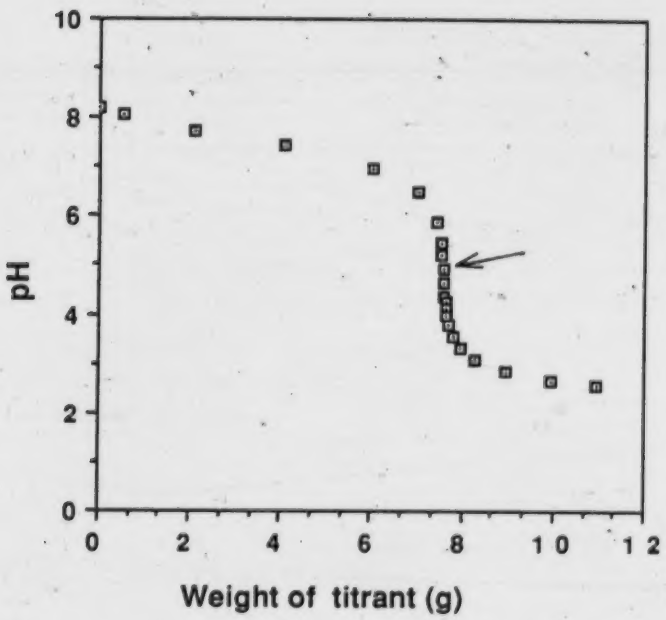
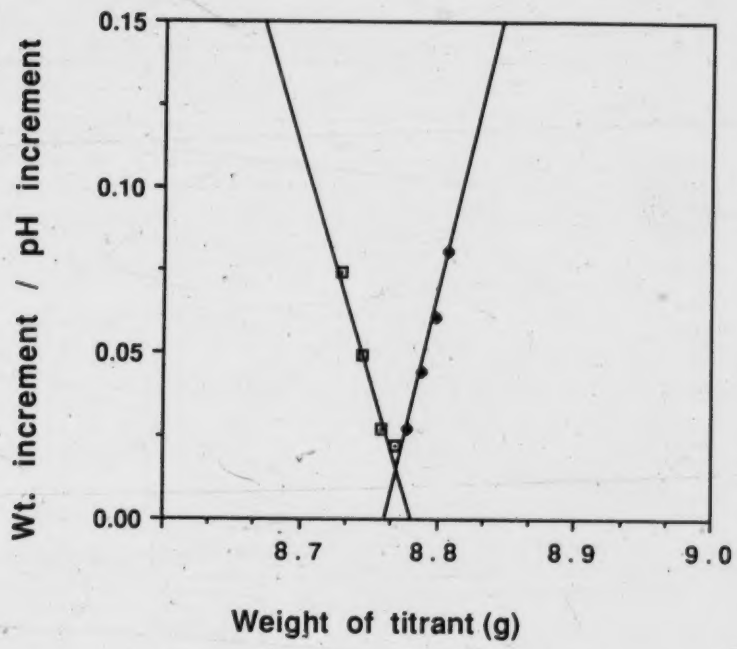


Figure 3. Titration curve of 5-nitrobenzimidazole in glacial acetic acid with perchloric acid in glacial acetic acid. Arrow indicates point at which crystal violet changed color. pH values are relative: True pH = (observed pH − 7).

point for a potentiometric titration may be established in any of several ways. The most straightforward method involves visual estimation of the midpoint in the steeply rising portion of the titration curve [94]. Another graphical approach involves a plot of the change in potential per unit change in volume of reagent ($\Delta E/\Delta V$) as a function of the average volume of reagent added. With both graphical techniques the assumption is made that the titration curve is symmetric about the true equivalence point, and that the inflection in the curve therefore corresponds to that point. This assumption is valid provided the participants in the chemical process react with one another in an equimolar ratio, and also provided the electrode process is perfectly reversible.

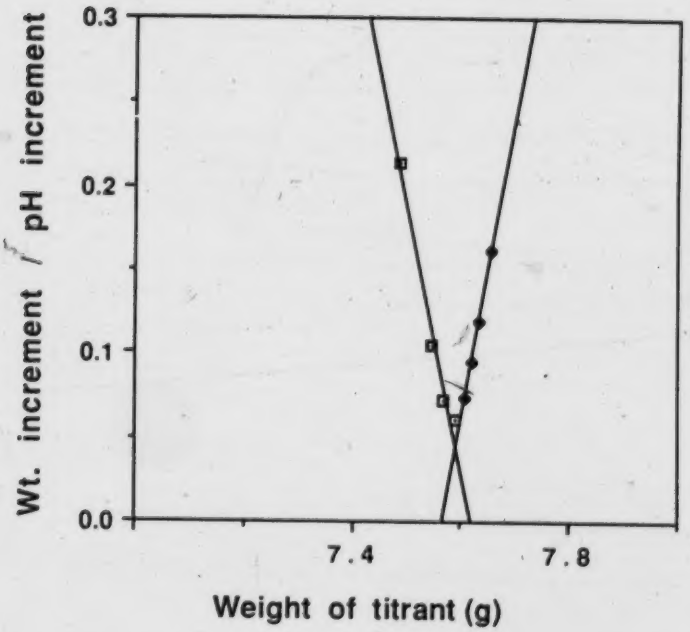
A less time consuming analytical method is to calculate the values of $\Delta E/\Delta V$ as the titration proceeds and to assume that this function is a maximum at the equivalence point. Lingane [95] has shown that the volume can be fixed more exactly by estimating the point where the second derivative of the potential with respect to volume (that is $\Delta^2E/\Delta V^2$) becomes zero. This is easily done if equal increments of solution are added in the vicinity of the equivalence point. The function becomes zero at some point between two volumes where a change in sign occurs and the volume corresponding to this point (obtained by interpolation) represents the equivalence volume. Another procedure consists of titrating to a predetermined equivalence point potential. Such a method demands that the equivalence point behavior of the system be entirely reproducible.

However, in this work the equivalence points were determined by the inverse-derivative plot method described by Ramette [96]. Figures 4 and 5



Equivalence point = 8.77

Figure 4. Inverse-derivative plot for the titration of benzimidazole in acetic acid with perchloric acid in glacial acetic acid.



Equivalence point = 7.59

Figure 5. Inverse-derivative plot for the titration of 5-nitrobenzimidazole in acetic acid with perchloric acid in glacial acetic acid.

show examples of inverse-derivative plots for titration curves of benzimidazole and 5-nitrobenzimidazole. An important advantage of this approach is that it allows good use of those points that are somewhat distant from the equivalence point. This is not possible with the nonlinear plots of the other graphical methods.

3.2 Results Obtained with Weight Titrations Using the Gravimetric Autotitrator Controlled by a Microcomputer

Percentage purity values of the benzimidazoles, shown in Table 5, were calculated from potentiometric equivalence points obtained with the inverse-derivative plot method. These results indicate a good reproducibility, and confirm the inverse-derivative plot as a precise method of detecting equivalence points. Comparison of the results of percentage purity obtained using the syringe as shown in Table 4 with those values obtained in the microcomputer-controlled titrations (Table 5) shows that more precise results are obtained with the latter method, as exemplified by the relatively smaller standard deviations. However, the percentage purity values obtained by both methods are close to each other for all the five benzimidazoles, and there is no difference between them at the 95% confidence level.

The indicators crystal violet and α-naphtholbenzein were each added to the separate microcomputer-controlled titrations to verify where their color changes occur within the break of the titration curve. It was found that in all cases the indicators did change color within the break, but slightly early, it took only a small quantity of titrant to cause this color change to occur. Table 5

Table 5. Percentage Purity of Recrystallized Substituted Benzimidazoles Determined by Microcomputer-Controlled Titrations in the Presence of Indicators.

Compound	% Purity		
		Indicator End Point	
	Potentiometric End Point	α-Napholbenzein	Crystal Violet
Benzimidazole	98.92±0.37[a]	98.84 ± 0.35	98.90 ± 0.12
2-Phenylbenzimidazole	99.12 ± 0.09	99.03 ± 0.11	98.99 ± 0.17
2-Methylbenzimidazole	99.70 ± 0.25	99.65 ± 0.27	99.00 ± 0.37
5-Nitrobenzimidazole	98.76 ± 0.25	98.46 ± 0.06	98.33 ± 0.01
5,6-Dimethylbenzimidazole	99.30 ± 0.14	99.28 ± 0.15	99.05 ± 0.16

[a]Uncertainties are 1 standard deviation based on duplicate titrations.

compares the percentage purity values obtained by the two indicators with the potentiometric values.

The titration curves obtained showed reasonable vertical breaks in the region of the equivalence point for all compounds except for 5-nitrobenzimidazole, in which the curve was somewhat drawn out. Figures 2 and 3, which show the titration curves of benzimidazole and 5-nitrobenzimidazole, confirm this observation. The pH values reported on the pH scale in the titration curves are not true pH values but are relative. The actual pH values would be equal to the observed pH values on the pH axes minus 7 pH units. It can be seen that there is a vertical break of 5 pH units in the region of the equivalence point for benzimidazole as compared to only a break of about 2.5 pH units for 5-nitrobenzimidazole. From the pK_a values 5-nitrobenzimidazole has a pK_a of 4.26 ($\mu = 0.05$) making it quite acidic and not sufficiently basic to produce a defined large, vertical break on titration with perchloric acid. This accounts for the break being small and drawn out in its titration curve.

4. CONCLUSIONS

The version of acetic acid reference electrode used in tnis potentiometric work was found to be satisfactory and reproducible. Sharp potentiometric equivalence points were detected for the titrations with the glass/reference electrode pair.

The inverse-derivative plot technique used to detect the equivalence points for the titrations proved quite successful. Percentage purity values for the benzimidazoles calculated from equivalence points obtained with this

technique were adequately reproducible. It can be concluded that the inverse-derivative plot provides a satisfactory method for detecting equivalence points.

The indicators α-naphtholbenzein and crystal violet have also been shown to be suitable for titrations of these benzimidazoles in acetic acid. Both changed color within the vertical break of the potentiometric titration curves and gave satisfactory end points, though both were slightly early. Of the two, α-naphtholbenzein is preferable because the color change was sharper and the end-point error somewhat smaller.

The titration curves obtained for the five benzimidazoles showed reasonable potential breaks of about 5 pH units for all the benzimidazoles titrated except for 5-nitrobenzimidazole, which had a short, drawn-out break that could not be used analytically. This confirms the weak basic character of 5-nitrobenzimidazole as compared to the other benzimidazoles studied. This conclusion was further confirmed by the low pK_a value determined for 5-nitrobenzimidazole, as described in the next chapter. For the practical purpose of preparing a benzimidazole unknown sample for instruction in nonaqueous titrations it is advisable to select from the other four benzimidazoles, all of which give larger vertical breaks in the region of the equivalence point.

CHAPTER IV

DETERMINATION OF IONIZATION CONSTANTS OF BENZIMIDAZOLE AND SUBSTITUTED BENZIMIDAZOLES BY UV SPECTROPHOTOMETRY

1. INTRODUCTION

The determination of benzimidazoles and related compounds by nonaqueous titration with perchloric acid depends on the compounds having sufficient base character that an adequate end point can be obtained. In connection with our interest in obtaining compounds with formula weights and base properties similar to those of benzimidazole for use in the preparation of mixtures suitable for analytical laboratory instruction as unknowns, we were interested in the dissociation constant values for the conjugate acids of these compounds.

The pK_a values of several substituted benzimidazoles under various conditions have been reported in the literature. The most complete study of ionization constants of substituted benzimidazoles, both in water and 50% aqueous ethanol, has been carried out by Davies *et al.* [23]. It is apparent from the literature that pK_a values obtained under different conditions vary considerably, so in order to establish any correlation among various substituted benzimidazoles the same conditions must be used. The choice of water as a solvent is preferable, of course, but too few benzimidazoles are sufficiently soluble in water to be useful for our purpose.

Methods for the determination of ionization constants in solution usually depend upon a quantitative assessment of the ratio of deprotonated/protonated forms for a compound under known conditions of acidity for the solvent medium. Although it is often possible to determine this ratio with high precision, the reliability of any of these methods depends ultimately upon the accuracy with which the appropriate acidity function can either be measured or assigned [97]. Analytical methods for the determination of the deprotonated/protonated ratio depend upon some difference in property or response that allows a quantitative discrimination to be made between the two forms of the compound. For example, using UV spectrophotometry, if a study of the spectrum (absorbance *versus* wavelength) of the pure deprotonated form obtained in a solution of high pH reveals significantly different features from a spectrum of the pure protonated form obtained at lower pH, then it is possible to deduce the ratio by measuring absorbances of solutions at values of pH that are intermediate between the upper and lower limits [97].

In this chapter, the base strengths of benzimidazole and four derivatives were studied by determining their pK_a values using a UV spectrophotometric method. Because some of the compounds were too insoluble in water to be studied directly, in this work a small amount of glacial acetic acid was used to dissolve the benzimidazoles under study. The solutions were then diluted with deionized water to the same volume, and sodium perchlorate was added to keep the ionic strength of the solution constant.

2. CALCULATION OF pK_a VALUES FROM SPECTRAL DATA

The method used will be discussed by considering the equilibrium reaction of protonated benzimidazole (BzH^+) with water and Beer's Law. The reaction may be represented as

$$BzH^+ + H_2O \rightleftharpoons Bz + H_3O^+$$

with K_a given by

$$K_a = \frac{[Bz][H_3O^+]}{[BzH^+]} \qquad (1)$$

Taking logs to base 10 of both sides and rearranging yields the expression

$$pK_a = pH + \log\frac{[BzH^+]}{[Bz]} \qquad (2)$$

For UV measurements Beer's Law, $A = \varepsilon bC$, may be applied, where A is absorbance, ε is molar absorptivity with units of liters per mole-cm; b is the path length of sample solution in cm and C is the concentration of the absorbing species in moles per liter. For b = 1 cm, as used in this work, $A = \varepsilon C$.

The total concentration C_T of the benzimidazole (Bz) is given by

$$C_T = \frac{(\text{Wt of Bz})}{(\text{Volume Stock Solution})(\text{Molecular wt Bz})}$$

and this is equal to the sum of the concentrations of the acidic (C_a) and basic (C_b) forms in solution, *i.e.*,

$$C_T = C_a + C_b \qquad (3)$$

The total absorbance A_T at a particular wavelength is equal to the sum of the absorbances contributed by the acidic (A_a) and basic (A_b) forms in solution. Hence

$$A_T = A_a + A_b \qquad (4)$$

since b = 1 cm, then

$$A_T = \varepsilon_a C_a + \varepsilon_b C_b \qquad (5)$$

Solving simultaneously equations (3) and (5) gives values for the concentrations of the protonated base [BzH^+], which is equal to C_a and the free base [Bz], which is equal to C_b.

Substituting these values of C_a and C_b into equation (2) at intermediate known pH values gives the pK_a.

3. EXPERIMENTAL

3.1 Apparatus

All pH values were measured using a Fisher-Accumet (Model 825 MP) pH meter which was equipped with a glass indicating electrode and a calomel reference electrode. The pH meter was calibrated against two standard buffers: (1) 0.05 *M* potassium biphthalate (pH 4.00 at 25°C) and (2) 0.05 *M* potassium-phosphate monobasic-sodium hydroxide (pH 7.00 at 25°C). The calibration was done each time before a set of pH values was measured.

Spectra were recorded on a Hewlett Packard 8451A diode array spectrophotometer in 1-cm silica cells thermostatted at 25 ± 0.2°C. Temperature control was achieved using a Lauda/Brinkman (K4R Electronic) circulator.

3.2 Chemicals and Solutions

The chemicals used were benzimidazole, 2-methylbenzimidazole, 5-nitrobenzimidazole, 2-phenylbenzimidazole, and 5,6-dimethylbenzimidazole (Aldrich Chemical Company), all recrystallized as described in Chapter II; perchloric acid (Fisher Scientific Company); ammonium hydroxide (British Drug House). All other inorganic reagents were reagent grade or better. Deionized distilled water was used throughout.

Two sets of four stock solutions (A, B, C, D) were prepared. One set was used to determine the pK_a at an ionic strength (μ) of 0.1 and the other set was used at an ionic strength of 0.05. Some measurements were also made at an ionic strength of 0.02 using solutions from set 2 and diluted to give the desired concentrations.

For μ = 0.1, the stock solutions were: (A) 0.1 g of recrystallized benzimidazole (or derivative) dissolved in 30 mL glacial acetic acid and diluted to 500 mL with deionized water; (B) perchloric acid solution (1 *M*) prepared by measuring 21.55 mL concentrated perchloric acid and diluting to 250 mL with water; (C) sodium perchlorate solution (1 *M*) prepared by dissolving 70.23 g of the salt in water and diluting to 500 mL with water; (D) ammonia solution (1 *M*) prepared by measuring 67.6 mL of concentrated ammonia into water and diluting to 1000 mL with water.

At μ = 0.05, the stock solutions were: (a) 0.1 g recrystallized benzimidazole (or derivative) dissolved in 15 mL glacial acetic acid and diluted to 500 mL with deionized water; (B) perchloric acid solution (0.5 *M*) prepared by measuring 10.8 mL concentrated perchloric acid and diluting to 250 mL with water; (C) sodium perchlorate solution (0.5 *M*) prepared by dissolving 35.12 g of the salt in water and diluting to 500 mL with water; (D) ammonia solution (0.5 *M*) prepared by measuring 33.8 mL of concentrated ammonia and diluting to 1000 mL with water.

A series of solutions having pH values between 1 and 10 were prepared from mixtures of solutions A, B, C, and/or D. Each resulting solution contained 10 mL of A. The most acidic solution, of pH about 1, was made up by mixing 10 mL of A and 10 mL of B. The most alkaline solution was prepared from a mixture of 10 mL A and enough D such that the pH of the solution was about 9. Solutions having pH values between these two extremes were then made up from A, C and D (*i.e.* mixing 10 mL A with varying quantities of C and D) such that the ionic strength was maintained at a fixed value of 0.1. The sodium perchlorate solution (C) was used only to adjust the ionic strength. Each

solution was ultimately diluted to 100 mL with deionized water. The acetic acid concentration of the final solutions was of the order of 1 percent or less by volume in all cases.

The pH of each solution was measured with calibrated electrode pair and pH meter, and then spectra were recorded over the wavelength range of 200 to 320 nm. The same procedure was used for the determination of pK_a values at ionic strengths of 0.05 and 0.02.

4. RESULTS AND DISCUSSION

4.1 Stoichiometric pK_a values of Benzimidazoles at Ionic Strengths of 0.05 and 0.1

Preliminary experiments on compounds sufficiently soluble in water that their pK_a's could be determined without resort to solvent mixtures showed that values obtained using a small amount of acetic acid were in good agreement with values previously determined in a 100% aqueous medium. Since the pK_a values reported in this work were determined under identical conditions, they may be compared among themselves.

Electron-donating groups such as alkyl and alkoxy groups *increase* the basic character of the benzimidazole systems, while electron-withdrawing groups such as nitro and phenyl groups *decrease* the basicity of benzimidazole. Substituent position is also an important factor in determining basicity, particularly in the case of substituents which act predominantly through an inductive effect. The effect of a substituent on the basicity of benzimidazole is stronger the closer this group is to the nitrogen atom. Groups in the 2-position are more effective in modifying the basic nature of the

imidazole ring than similar groups in the 5(6)-position. This is illustrated by the fact that 2-methylbenzimidazole (pK_a 6.19) is more basic than 5,6-dimethylbenzimidazole (pK_a 5.98).

Preliminary studies on the UV spectra of acetic acid and sodium acetate showed that these two compounds absorb between 200 to 230 nm. Thus the pK_a values determined in this wavelength range would not be very reliable and could be biased. Therefore the pK_a values reported in this work were all determined in the wavelength range of 240 to 300 nm. Figures 6 to 10 show the UV spectra of the benzimidazoles (concentration ~1.5×10^{-3} *M*) recorded over a wavelength range of 200-300 nm. Results for those compounds previously measured were found to agree within ±0.20 pK unit with literature values shown in Table 6. The slight differences in the pK_a values reported in this work and literature values may be attributed at least in part to differences in ionic strength.

Determination of the pK_a values of 2-phenylbenzimidazole and 5-nitrobenzimidazole in water was not experimentally possible with the potentiometric method used by Davies [23] owing to the insolubility of these two compounds in water. Our method using sufficient acetic acid to facilitate solubility gave pK_a values for these compounds of 5.13 at $\mu = 0.05$ and 5.28 at $\mu = 0.1$ for the 2-phenyl derivative and 4.26 at $\mu = 0.05$ and 4.35 at $\mu = 0.1$ for the 5-nitro derivative all measured at 25 ± 0.2°C. These values seem reasonable when compared to those for the parent benzimidazole, 5.54 at $\mu = 0.05$ and 5.66 at $\mu = 0.1$. This is because the phenyl and nitro substituents produce an inductive effect which reduces the availability of electrons on the

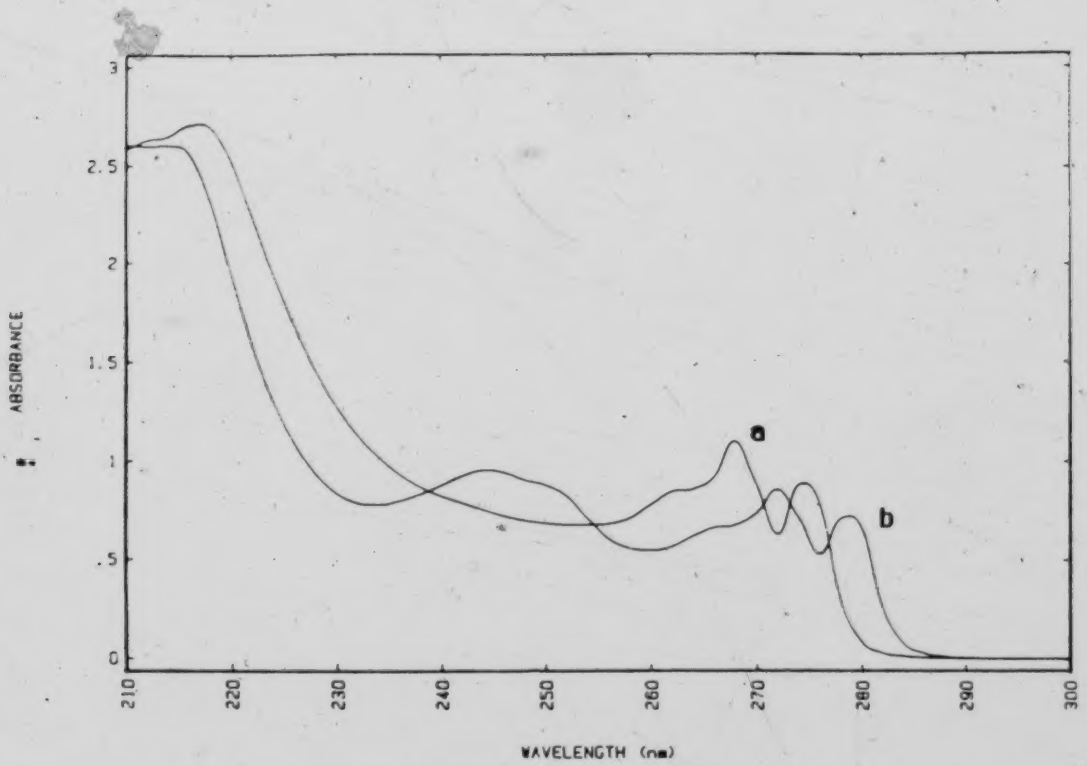


Figure 6. UV spectra of acidic (a) and basic (b) solutions of benzimidazole.

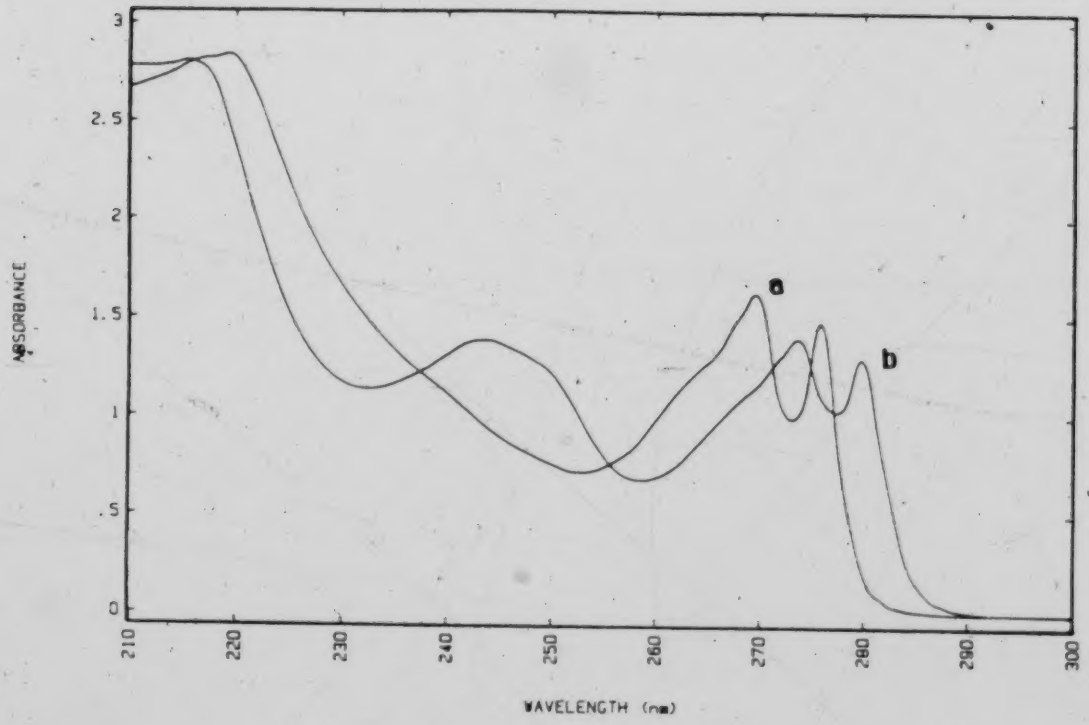


Figure 7. UV spectra of acidic (a) and basic (b) solutions of 2-methylbenzimiazole.

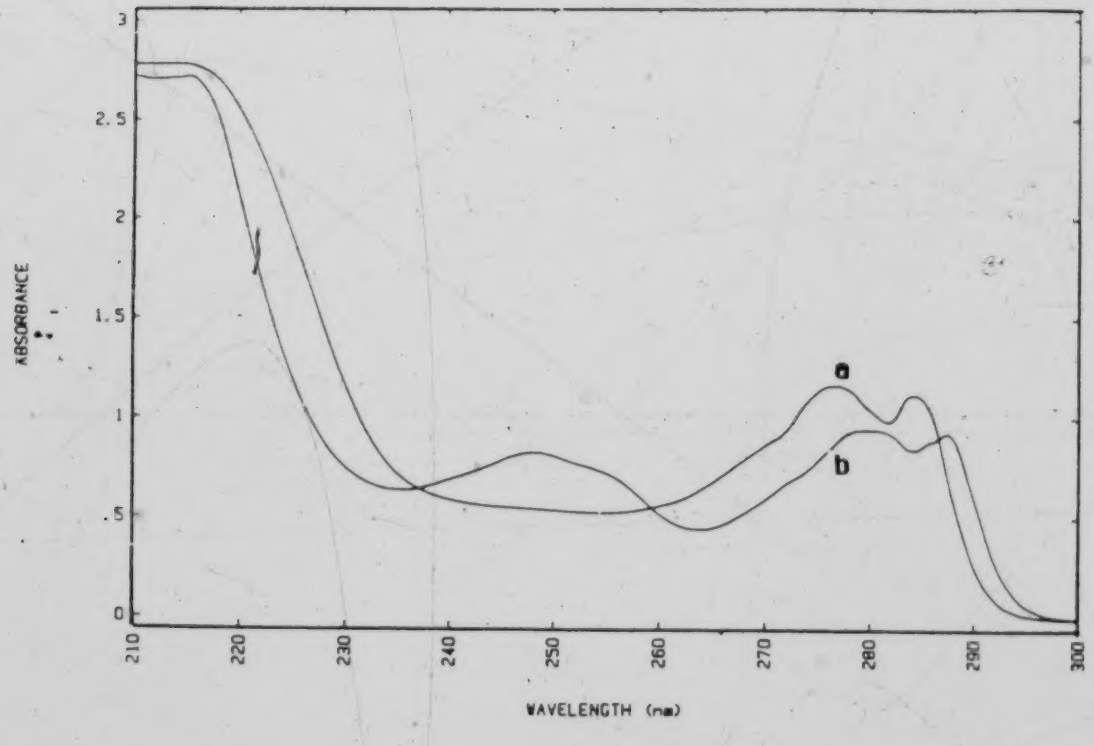


Figure 8. UV spectra of acidic (a) and basic (b) solutions of 5,6-dimethyl-benzimidazole.

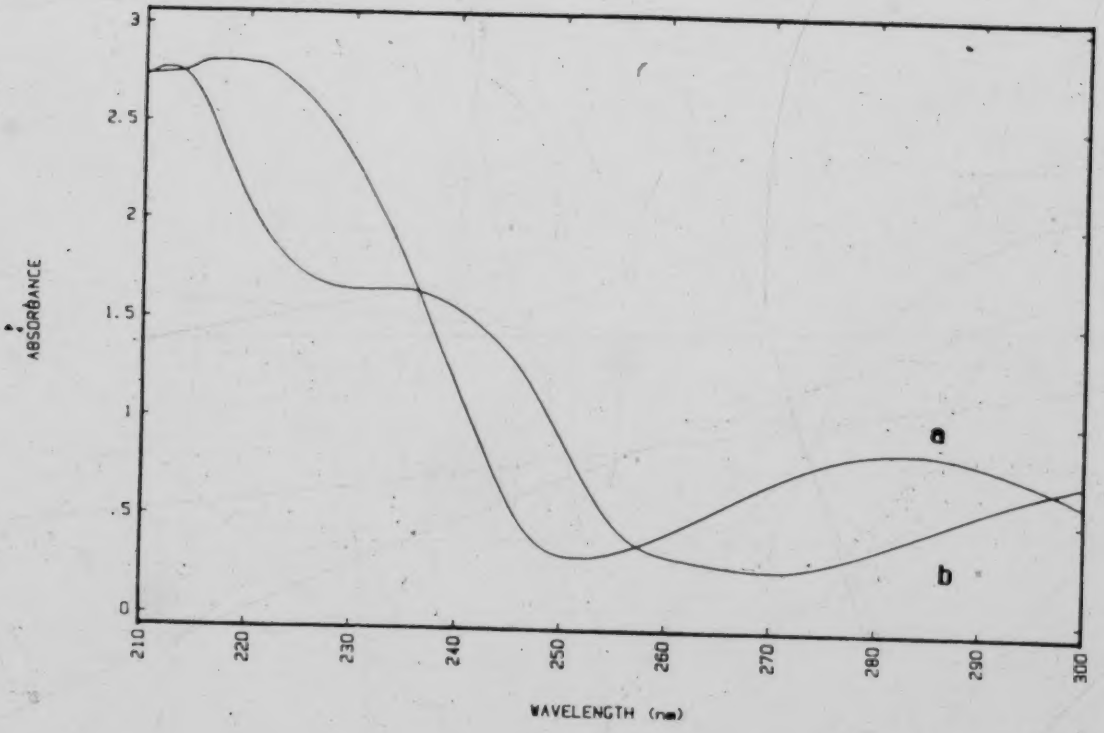


Figure 9. UV spectra of acidic (a) and basic (b) solutions of 5-nitrobenzimidazole.

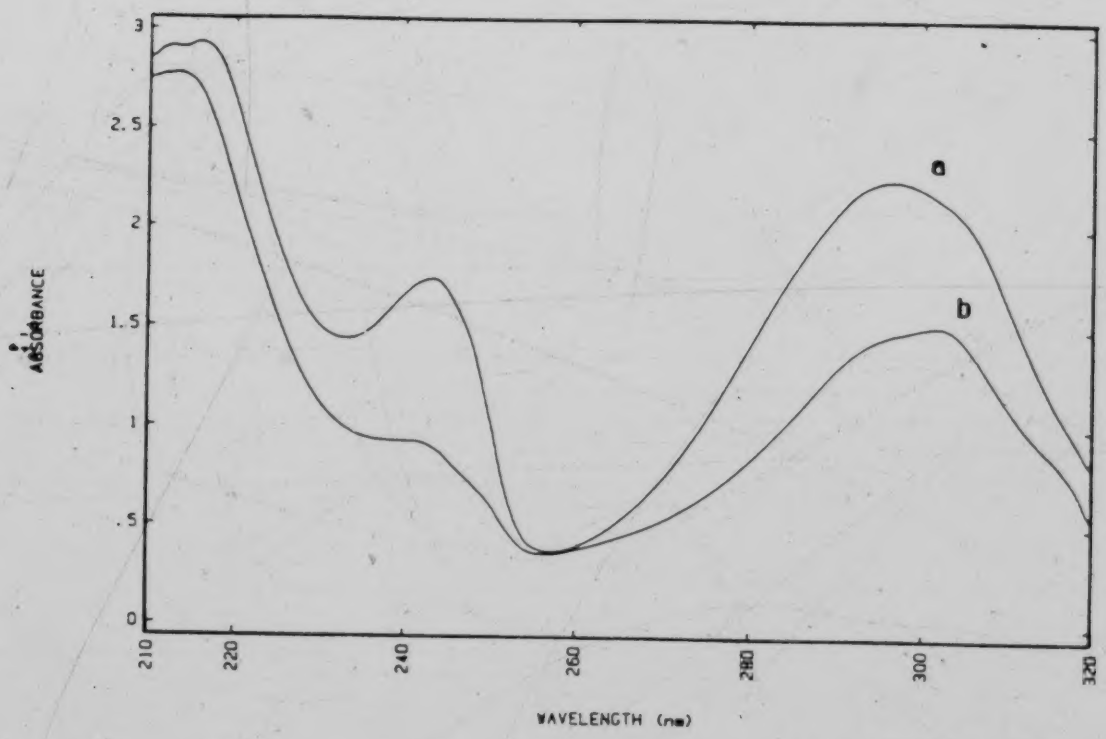


Figure 10. UV spectra of acidic (a) and basic (b) solutions of 2-phenyi-benzimidazole.

Table 6. Available Literature pK_a Values of Benzimidazole and Substituted Benzimidazoles. Data from Refs. 23 and 24.

	pK_a	
	In water at 25 ± 1°C [23]	In 5:95 EtOH:H_2O at 30 ± 0.5°C [24]
Benzimidazole	5.53/5.48	5.52
2-Phenylbenzimidazole	—	5.33
5-Nitrobenzimidazole	—	4.50
2-Methylbenzimidazole	6.19	6.10
5,6-Dimethylbenzimidazole	5.98	5.99

basic nitrogen, thereby lowering the basicity of the parent benzimidazole. Concerning the relative decrease in basicity of benzimidazole by the 2-phenyl and 5-nitro groups, Davies' [23] data in aqueous ethanol shows that the 5-nitro group decreases the basicity to a greater extent than the 2-phenyl substituent. This is parallelled in our work. Furthermore, Davies [23] compared the basicity values in aqueous ethanol of a series of benzimidazoles containing a common substituent with the pK_a values of the corresponding benzimidazoles without that substituent and observed that the effect of the substituent on the basicity of the benzimidazole (δpK_a) is essentially constant. Thus a 2-methyl group elevates the basicity of benzimidazole itself by 0.79 units and a 5,6-dimethyl group causes an increase of 0.52 units. The 2-phenyl and 5-nitro groups decrease the basicity of benzimidazole by 0.42 and 2.31 units respectively. Extensive comparisons of this kind led Davies to the following list of δpK_a values:

Substituent	δpK_a
2-methyl	+0.79
5,6-dimethyl	+0.52
5-methyl	+0.31
5-methoxy	+0.15
benzimidazole (parent)	0.00
1-methyl	-0.04
2-phenyl	-0.42
5-chloro	-1.04
5-nitro	-2.31

Employing these constants, the pK_a value (in aqueous ethanol) of a substituted benzimidazole could be calculated by adding the δpK_a values of the substituents to the value of pK_a for the parent base (4.98). Polar interactions between the substituents were thus shown to be of a low order. Interaction between the electronic patterns of benzimidazole and substituent groups is evident, however, as the δpK_a values of the latter vary markedly with their position within the benzimidazole framework.

The δpK_a values presented in Table 7 were obtained from pK_a values determined in our work in aqueous acetic acid. The results show that the values are close to each other at the two ionic strengths. This confirms the observation established earlier by Davies [23] that the effect (δpK_a) of the substituent on the basicity of benzimidazole is essentially constant.

The pK_a values at ionic strengths of 0.05 and 0.1 for the compounds studied are shown in Tables 8 and 9. Values at the two ionic strengths were found to be within 5% of each other. However, values at ionic strength of 0.1 were slightly greater than values at ionic strength of 0.05. This difference is likely due to salt effects causing a variation in activity coefficients at different ionic strengths. The pK_a values were also determined for three of the compounds—benzimidazole, 2-methylbenzimidazole and 5,6-dimethylbenzimidazole—at an ionic strength of 0.02 and values shown in Tables 8 and 9. This was done in order to verify the linearity of plots of log K_a *versus* $\sqrt{\mu}$ used to obtain pK_a values at zero ionic strength as described in Chapter IV, Section 4.2. The pK_a values obtained for these three benzimidazole compounds agree closely with the values reported by Davies [23].

Table 7. δpK_a Values of the Substituents of Benzimidazole at Ionic Strengths of 0.05 and 0.1.

	δpK_a	
Substituent	$\mu = 0.05$	$\mu = 0.10$
2-Methyl	+0.59	+0.62
5,6-Dimethyl	+0.44	+0.45
2-Phenyl	-0.40	-0.34
5-Nitro	-1.31	-1.27

Table 8. pK_a values for Substituted Benzimidazoles as a Function of Ionic Strength (μ) at 25 ± 0.2°C as Determined by UV Spectrophotometry. Replicate Values are Based on Measurements of Independent Solutions on Separate Days.

	$\mu = 0.02$	$\mu = 0.05$	$\mu = 0.10$
Benzimidazole	5.47 ± 0.09 (7)[a]	5.55 ± 0.14 (5)	5.69 ± 0.17 (4)
	5.45 ± 0.09 (9)	5.52 ± 0.17 (9)	5.62 ± 0.12 (10)[a]
2-Methylbenzimidazole	6.13 ± 0.20 (8)	6.16 ± 0.02 (6)	6.21 ± 0.04 (8)
	6.14 ± 0.11 (8)	6.16 ± 0.13 (6)	6.26 ± 0.12 (9)
5,6-Dimethylbenzimidazole	5.93 ± 0.07 (9)	5.97 ± 0.13 (9)	6.03 ± 0.14 (8)
	5.92 ± 0.10 (8)	5.99 ± 0.21 (9)	6.10 ± 0.08 (8)
5-Nitrobenzimidazole	—	4.27 ± 0.18 (8)	4.30 ± 0.18 (8)
		4.24 ± 0.21 (10)	4.39 ± 0.20 (11)
2-phenylbenzimidazole	—	5.14 ± 0.26 (6)	5.36 ± 0.07 (4)
		5.12 ± 0.10 (9)	5.20 ± 0.25 (9)

[a]Uncertainties are standard deviations based on the number of spectral points (given in parentheses) used in equation 2 for a given solution series.

Table 9. Summary of Average pK_a Values of Benzimidazoles Based on Measurement of Independent Solutions on Separate Days. Two Replicates Done on Each Compound as Shown in Table 8. Uncertainties are 95% Confidence Limits.

	$\mu = 0.02$	$\mu = 0.05$	$\mu = 0.10$
Benzimidazole	5.46 ± 0.01	5.54 ± 0.02	5.66 ± 0.05
2-Methylbenzimidazole	6.14 ± 0.01	6.16 ± 0.00	6.24 ± 0.04
5,6-Dimethylbenzimidazole	5.93 ± 0.01	5.98 ± 0.01	6.07 ± 0.05
5-Nitrobenzimidazole	—	4.26 ± 0.02	4.35 ± 0.06
2-Phenylbenzimidazole	—	5.13 ± 0.01	5.28 ± 0.11

4.2 Determination of Thermodynamic Equilibrium Constants

By measuring stoichiometric equilibrium constants over a range of ionic strengths and plotting the data as some function of ionic strength, it is possible to obtain thermodynamic equilibrium constants. Ideally, if thermodynamic equilibrium constants are to be obtained by extrapolation to zero ionic strength, they should be obtained from measurements in two different ionic media, since agreement in the two media will ensure that no specific effects due to the background electrolytes are present [98]. Also, the ionic strengths should be as low as possible to reduce error. A number of techniques for extrapolating to zero ionic strength have been suggested, varying from plotting log K against the ionic strength (μ) itself, through plotting log K against $\mu^{1/2}$ or $\mu^{1/3}$, to plotting complex functions such as log K against μ or $\mu^{1/2}$ [95], where log K° is given by

$$\log K^{\circ} = \log K - \frac{Az+z\cdot\sqrt{\mu}}{1+aB\sqrt{\mu}} - C\mu$$

This equation is obtained by combining an extended form of the Debye-Hückel equation

$$-\log \gamma_{\pm} = \frac{az+z\cdot\sqrt{\mu}}{1+aB\sqrt{\mu}} - C\mu$$

where a, A, B, and C are all constants, some or all of which may be treated as adjustable parameters, with the equation representing the thermodynamic

equilibrium constant ($K^{\ominus}$) in terms of both concentration and activity coefficients. For the reaction

$$BzH^+ + H_2O \rightleftharpoons Bz + H_3O^+$$

$K^{\ominus}$ is given by

$$K^{\ominus} = \frac{a_{Bz}a_{H_3O^+}}{a_{BzH^+}} = \frac{[Bz][H_3O^+]}{[BzH^+]} \frac{\gamma_{Bz}\gamma_{H_3O^+}}{\gamma_{BzH^+}}$$

In this work thermodynamic equilibrium constants were determined by plotting log K against μ and log K against $\mu^{1/2}$ as shown in Figures 11 and 12. The graph for Figure 11 can be expressed by an equation of the form

$$\log K_a = \log K_a^{\ominus} + \beta\mu$$

in which β is a constant which represents the slope of the curve. Extrapolation of the least squares line to $\mu = 0$ yields an intercept equal to the value of the thermodynamic log K_a. Values obtained for the five benzimidazole compounds studied are reported in Table 10. From Figures 11 and 12 the plot of log K *versus* μ is the more linear of the two techniques of extrapolation, and the thermodynamic pK_a values obtained agree closely with the literature values for those compounds previously measured. The plots of log K *versus* square root of ionic strength yielded lower values (as shown in Table 10), were less linear, and in addition the pK_a values obtained were in poorer

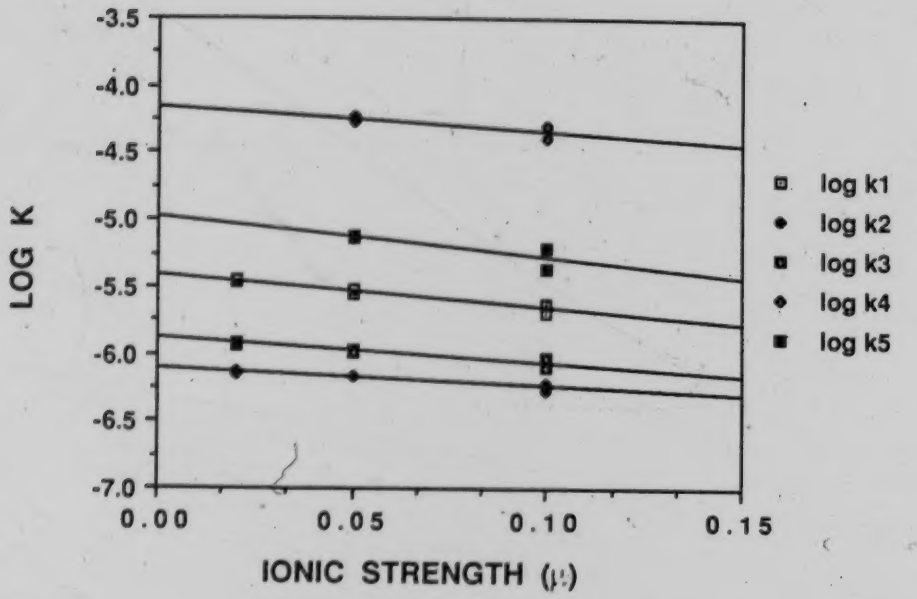


Figure 11. Plot of log K *versus* ionic strength for the benzimidazoles. Log k1, benzimidazole; log k2, 2-methylbenzimidazole; log k3, 5,6-dimethylbenzimidazole; log k4, 5-nitrobenzimidazole; log k5, 2-phenylbenzimidazole.

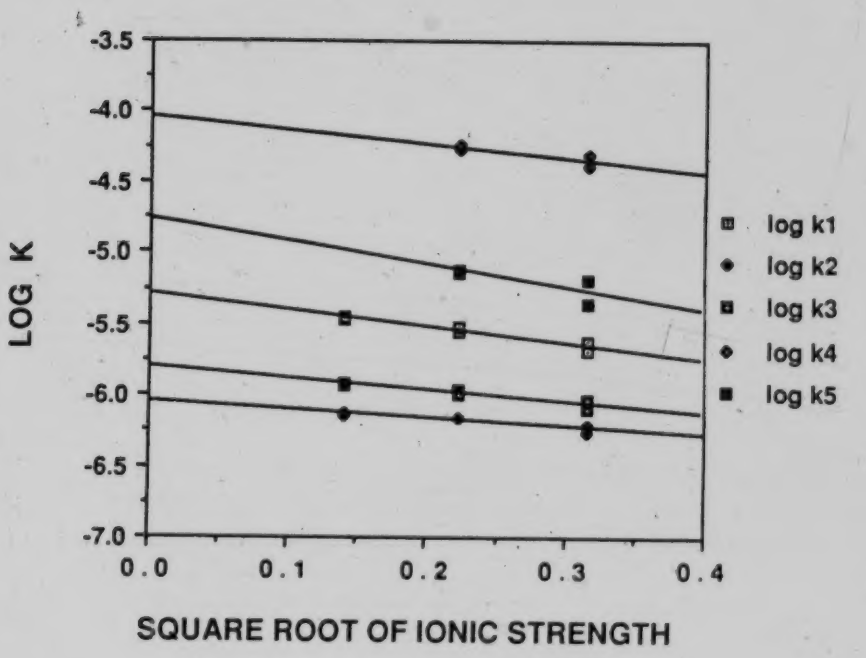


Figure 12. Plot of log K *versus* square root of ionic strength for the benzimidazoles. Log k1, benzimidazole; log k2, 2-methylbenzimidazole; log k3, 5,6-dimethylbenzimidazole; log k4, 5-nitrobenzimidazole; log k5, 2-phenylbenzimidazole.

Table 10. Thermodynamic pK_a Values for Benzimidazole and Substituted Benzimidazoles as Determined Spectrophotometrically in Aqueous Acetic Acid at 25°C by Extrapolation from Figures 11 and 12. Uncertainties are 95% Confidence Limits.

Compound	pK_a Values	
	log K *vs* μ	log K *vs* $\mu^{1/2}$
Benzimidazole	5.41 ± 0.02	5.30 ± 0.04
2-Methylbenzimidazole	6.10 ± 0.02	6.05 ± 0.03
5,6-Dimethylbenzimidazole	5.89 ± 0.02	5.81 ± 0.04
5-Nitrobenzimidazole	4.17 ± 0.07	4.04 ± 0.14
2-Phenylbenzimidazole	4.98 ± 0.12	4.77 ± 0.24

agreement with the literature values than those obtained by a log K *versus* μ plot. The coefficient of correlation (r) was used to decide which of the two plots is more linear. The plots of log K *versus* μ were found to have r values closer to unity (1) as compared to the plots of log K *versus* square root or ionic strength. Hence the plot of log K *versus* μ is considered the more linear plot.

5. CONCLUSIONS

The basic strengths of five benzimidazoles have been studied by measuring spectrophotometrically their pK_a values at ionic strengths of 0.02, 0.05, and 0.1 in aqueous highly dilute acetic acid at 25°C. The use of sufficient acetic acid to enhance solubility of these benzimidazole compounds enabled us to determine pK_a values by UV spectrophotometry for 5-nitrobenzimidazole and 2-phenylbenzimidazole, which is not experimentally possible with 100 percent aqueous potentiometric methods owing to the insolubility of these two benzimidazoles in water. The pK_a values of the five benzimidazoles at different ionic strengths were extrapolated to zero ionic strength to obtain thermodynamic pK_a values. The results for those compounds previously measured were in close agreement with literature values.

Two techniques for extrapolating to zero ionic strength were used in this work: log K *versus* μ and log K *versus* $\sqrt{\mu}$. We found plots of log K *versus* μ to be more nearly linear and also to give thermodynamic pK_a values which were in better agreement with literature values for previously measured substances.

CHAPTER V

FUTURE WORK

In this work, a number of benzimidazoles have been determined in acetic acid by weight titrations using perchloric acid as titrant with two indicators, α-naphtholbenzein and crystal violet. These two indicators have been found not significantly different at the 95% confidence level and can be considered to give the same results within experimental error. These indicators were also found to be suitable by observing their behavior during automatic potentiometric titrations carried out on these benzimidazoles. Both indicators changed color within the potential break in the region of the equivalence point. Visually the color change of α-naphtholbenzein was sharper and more satisfactory, however. The inverse-derivative plot method used to detect equivalence points in the automatic potentiometric titrations was satisfactory and gave results which were adequately reproducible. The nonaqueous acid-base titration procedure developed here could be applied to other benzimidazoles and related bases.

The compounds studied here could be used to develop a wide range of mixtures as unknowns for instruction in an analytical teaching laboratory. It could also be useful to examine the use of other nonaqueous solvents, titrants, and end-point detection techniques in the titrations of other benzimidazole compounds.

With a knowledge of the pK_a values of the benzimidazoles it would be worth investigating the possibility of automatic differential titrations of mixtures

of these benzimidazoles. Another useful study would be to apply nonaqueous weight titrations to micro- and ultramicrodeterminations of benzimidazoles. In this method the quantity of solvent used is kept to a minimum and this leads to improved end-point recognition. The special apparatus used permits a marked reduction of the titration volume and also the titrant solution can be measured with an accuracy of a fraction of a microliter.

Despite the wide range of important applications of benzimidazoles, their pK_a values have not been extensively determined in the past. Thus it would be useful to apply the UV spectrophotometric method used successfully here to determine and compile the pK_a values of other benzimidazoles. This would provide additional information on their basic strengths, useful for interpretation of pH titrations where multiple acidic or basic sites are present, especially in preparative laboratories where yields and purification might be improved by utilizing knowledge of pK_a values.

Two extrapolation techniques have been evaluated in this study to determine the pK_a values at zero ionic strength. The linearity of both plots were satisfactory. It is recommended that other extrapolation techniques are considered to determine thermodynamic pK_a values of these benzimidazoles and to compare the values obtained.

The temperature has been maintained constant at 25°·C in the present work. The determination of ionization constants at different temperatures would provide quantitative information on the effect of temperature on the ionization constants of benzimidazoles and to determine the dpK_a/dT coefficient and entropy which is of thermodynamic importance.

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